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From the Baker Clinic Research Laboratory, New England Deaconess Hospital, and the Joslin Clinic, Boston, Massachusetts.

The Bulbar Conjunctival Vascular Bed in Diabetic Children

by JØRN DITZEL and JANINE DUCKERS

The use of insulin, chemotherapeutics and antibiotics has considerably prolonged the life expectancy of diabetic children. The greater longevity has, however, been accompanied by an increasing occurrence of severely disabling retinopathy and nephropathy. The discovery of the cause(s) of the generalized degeneration of the smaller blood vessels is an urgent problem in diabetes.

In vivo investigations using a technique which makes possible the observance of the small blood vessels at the microscopic level might therefore be valuable in elucidating some factors involved in the pathogenesis of the vascular disease. Application of the stereoscopic dissecting microscope to the study of the smaller blood vessels of the bulbar conjunctiva appears suitable for this purpose. Recently the results of such *in vivo* observations of the smaller blood vessels and the circulating blood in adult diabetics were reported (4). The study showed that many cases of diabetes, including some of short duration, exhibited characteristic functional and morphological changes in the conjunctival vascular bed. The vascular abnormalities included arteriolar constriction and venular distension associated with exudation, intra-arteriolar aggregation of red cells, and slowing of linear velocity of cell flow. Serial observations for months in young diabetics proved these changes to be reversible. Other changes such as tortuous elongations of the venous part of the capillaries and of the venules and perivascular "hyaline" infiltrations were shown to be irreversible (7, 8).

Since in the children the vascular bed has been little influenced by the changes associated with aging, observations in the young patient should give the most lucid picture of the effect of diabetes *per se*. The purpose of the present study was to evaluate the incidence, nature and cause of the changes in the vascular bed of the bulbar conjunctiva of diabetic children.

Aided by grants from the National Institutes of Health (A-H-1070), the Massachusetts Lions Eye Research Fund and the Danish State Research Foundation.

Materials and Methods

The material consisted of 140 children. Seventy diabetic children were recalled for special investigation and were compared with 70 non-diabetic children. The children were evenly divided as to sex and their ages varied from 6–17 years. The only selection of the diabetic children examined was due to that of geographical location, i.e., those living in close proximity to the New England Deaconess Hospital. All the diabetic children received insulin; usually a small amount of crystalline mixed with NPH insulin. The total insulin dose varied from 20 to 132 units daily. Seventy-one per cent was given more than 30 I.U. Retinopathy and evidence of nephropathy was known to be present in only one patient. At the time of the examination, all degrees of control were present. Blood sugars (Folin-Malmros (9)) were determined in 19 of the diabetic children and the values varied from 82–458 mg per 100 ml. However, all the diabetic children felt well.

The control group consisted of non-diabetic "healthy" children. The boys were chosen from a school near the hospital and the girls were visitors to the Dental Out-Patient Clinic at the Children's Medical Center, Boston. They were selected according to age and sex in order to compare them with similar groups of diabetic children. Precautions were taken in all children to rule out local conjunctival irritation and all kinds of infections (including colds), since these conditions might cause changes in the vascular bed irrelevant to this particular study.

In Table 1 the pertinent data are given on *all* children with regard to sex and age at examination, and for the *diabetic* children, age at onset of diabetes, duration of diabetes, and insulin dose. It is evident from the figures that each diabetic group is comparable to its control group with regard to average age.

To make it possible to compare the diabetic boys with the diabetic girls, analyses were made of the distribution of the age at onset of diabetes, age at the examination, duration of the diabetes, and insulin dose.

The incidence of diabetes in the near relatives (parents, grandparents, brothers and sisters) of the diabetics was 37 per cent among the boys and 26 per cent among

TABLE 1

The composition of the total material with regard to number, sex, age at onset of diabetes, age at examination, duration of diabetes and insulin dose.

Diabetics							Controls		
Number of cases	Sex	Age at onset of diabetes (yrs. ± s.d.)	Age at examination (yrs. ± s.d.)	Duration of diabetes (yrs. ± s.d.)	Insulin dose (I.U.)	Number of cases	Number of cases	Sex	Age at examination (yrs. ± s.d.)
					< 30	13			
35	M	6.1 ± 3.3	11.3 ± 3.3	5.9 ± 3.4	30–60	15	35	M	10.8 ± 2.8
					> 60	7			
					< 30	9			
35	F	6.7 ± 2.8	10.7 ± 2.6	4.3 ± 2.7	30–60	16	35	F	9.9 ± 2.4
					> 60	10			

TABLE 2

Result of the estimate of the diabetic control.

Sex	Diabetic Control			
	"Good"		"Poor"	
	Number	Per cent of estimated cases	Number	Per cent of estimated cases
M	12	40	18	60
F	14	54	12	46
Total	26	47	30	53

the girls. The degree of long-term control of diabetes was estimated in each case after a thorough interview with the parents regarding the care of the child, the dietary and insulin treatment and the daily urine specimens. It was felt that it was possible only to divide this series into terms of "good" and "poor" control. In 14 cases it was impossible to give even an approximate estimate of the degree of control. The degree of "good" control was generally assigned to children whose diet was weighed, who had consistent daily blue or green urine tests, had never had diabetic coma and who had visited a doctor regularly. Since most of the children were not under regular supervision at the Joslin Clinic, this evaluation has been considered inadequate for analysis of the relationship between control and vascular conjunctival changes. The result of the estimate of control is given in Table 2. A X^2 test of the distribution of the "badly-controlled" and the "well-controlled" showed that there was no significant difference between the sexes.

Since also the age at onset of diabetes, chronological age, duration of diabetes and insulin dose were found to be evenly distributed, the two sex groups of diabetic children were found to be comparable.

To omit bias in this study, all conjuctival examinations were carried out by the same observer who knew nothing about the medical history of the diabetic children. At the completion of the study the conjuctival findings were compared with the results of the medical history. Information about the method for studying the conjunctival vessels and about the terminology used has been given previously (4–8).

Results

The Vascular Pattern in the Bulbar Conjunctiva of Non-Diabetic "Healthy" Children

Although considerable variation existed in the arrangement of the smaller blood vessels in the bulbar conjunctiva from subject to subject, certain characteristics of the vessel walls and the blood flow were invariably the same. The picture of the combined vascular and hemodynamic pattern of the "healthy" children could be well defined by these characteristics.

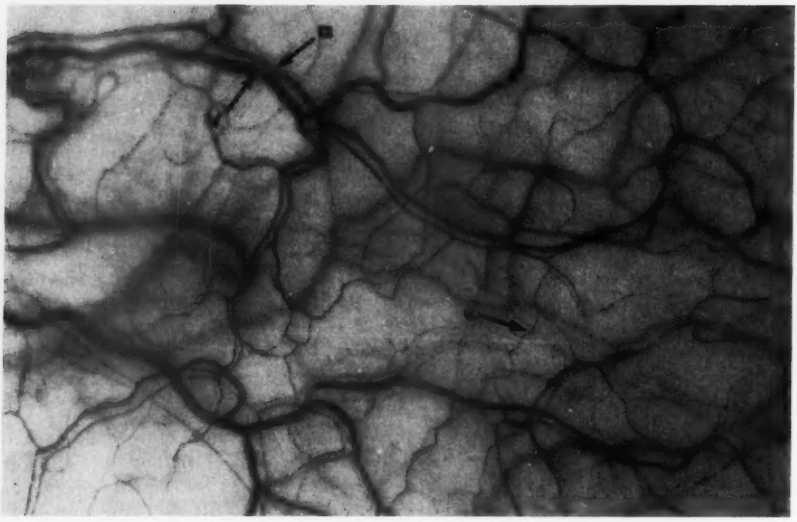

Fig. 1. The conjunctival vascular bed of a "healthy" child (14 years). Characteristics: (1) the smaller blood vessels show regular configuration; (a) arteriole, (c) capillary, (v) venule. (2) the A:V ratio is 1:3–1:2. (3) no intravascular erythrocyte aggregation (4) no edema. 45 ×.

The arterioles were often found to enter the conjunctiva parallel to larger venules, to decrease in caliber and to branch dichotomously, giving rise to terminal arterioles. The capillaries could be seen to branch from the tip of the arterioles, and although no definite pattern might be observed, the capillary network was regular and well ordered. The capillaries, in general, were straight or showed a delicately winding course, and no irregularities such as angular tortuosities, nodularities or localized dilatations were seen. The capillaries usually had anastomoses with one another and finally drained into the venular system (Fig. 1). Besides these "true" capillaries, it was often possible to follow a terminal arteriole more directly into a venule through a non-anastomosing vascular channel which was somewhat wider than the "true" capillaries. When the capillaries themselves were closed, these channels were of such capacity that they permitted passage of large amounts of blood into the venules. These communications should not be mistaken for the so-called arterio-venous anastomoses. Their different placement in the vascular bed is illustrated in Fig. 2. Observations made in this study indicated that the direct arteriolar-venular communication served functions significantly different from those of the presumptive "true" capillaries. Such a functional difference was recently suggested by Meighan (15).

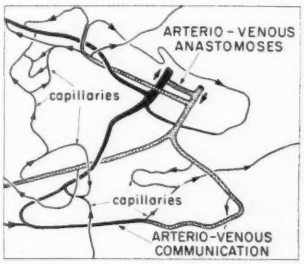

Fig. 2. The different placement of the "arterio-venous communication" and the "arterio-venous anastomosis". Arterio-venous anastomosis is a rare finding in the conjunctival vascular bed.

The larger venules, which showed smooth curves and increasing diameter, were usually situated somewhat superficially to the accompanying arterioles. Under physiological conditions the ratio between the diameter of the arteriole and that of the accompanying venule was relatively constant, and was 1:3–1:2.

The study of the circulating blood in "healthy" children showed that the circulating blood cells were not aggregated. The blood flow was laminar and usually followed the same pathways so that the over-all figurative pattern of the vascular bed over a period of time was remarkably constant. The rate of flow in the arterioles and larger venules, measuring approximately 60–120 micra, was so rapid that individual red cells were not distinguishable. The blood cells did not stick to the wall of the smaller vessels and the small vessels did not leak appreciable amounts of fluid. These observations were in close agreement with the findings by Lee & Holze (13) and confirmed our earlier studies in non-diabetic young adults.

Abnormal Vasomotor Changes in the Peripheral Vascular Bed of the Bulbar Conjunctiva in Diabetic Children

When the combined vascular and hemodynamic patterns observed in the diabetic were compared with that of the "healthy" children, two well-defined functional deviations from the normal were observed and have here been designated as Vascular Pattern-Change I and Vascular Pattern-Change II of the smaller blood vessels. These two pattern changes were apparently various degrees of a vasomotor reaction, Vascular Pattern-Change II being the more severe (Figs. 3–8).

Vascular Pattern-Change I is illustrated in Figs. 4, 5 and 6. This change was characterized by a general distension occasionally associated with fusiform dilatations of the larger venules. The diameters of the arterioles were usually unchanged, occasionally slightly narrowed and the arteriolar/venular diameter ratio was consequently variably decreased from 1:4 to

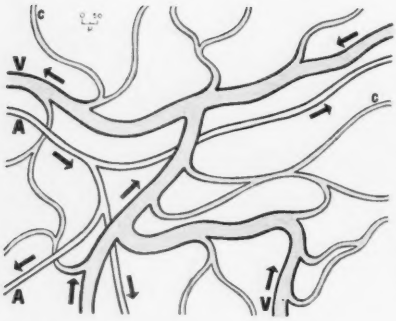

Fig. 3. Normal vascular pattern.

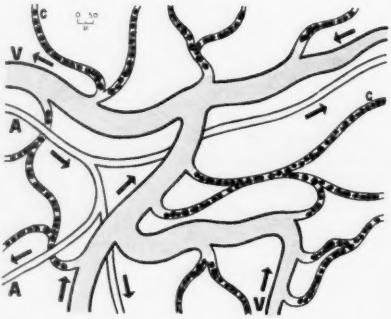

Fig. 4. Vascular Pattern-Change I, Grade 1.

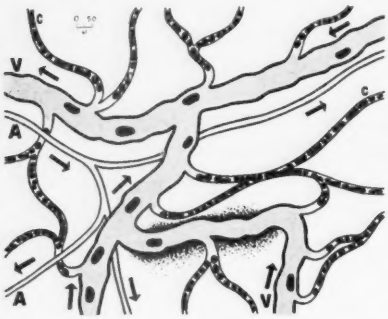

Fig. 5. Vascular Pattern-Change I, Grade 2.

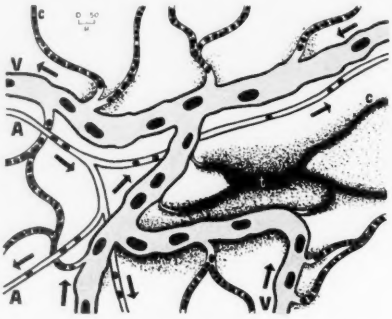

Fig. 6. Vascular Pattern-Change I, Grade 3. (t) micro-thrombosis in venous part of capillaries.

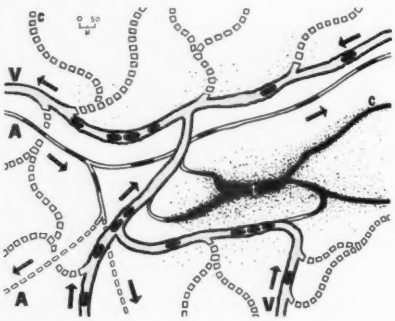

Fig. 7. Vascular Pattern-Change II. (t) micro-thrombosis in venous part of capillaries.

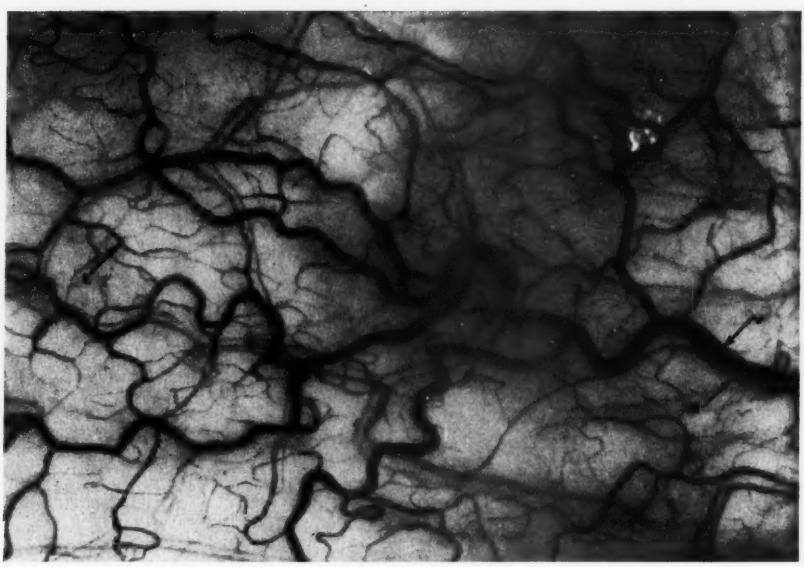

Fig. 8. The conjunctival vascular bed of a diabetic child (age 15 years, duration of diabetes 6 years) showing Vascular Pattern-Change I. Note the distended, elongated and congested venules. A:V ratio is 1:6. Also some capillaries are distended (c). 35 ×.

1:7 (Fig. 8). Concentration of the passing blood could occasionally be observed in the smaller venules, indicated by darkening in color and a pasty consistency of the blood. The circulating red cells were aggregated into clumps of various sizes and rigidity. Simultaneously the linear rate of blood flow was decreased, particularly in the capillaries and in the smaller venules. Localized edema was often present at the same time in the perivascular conjunctival tissue (Fig. 9).

Vascular Pattern-Change II is illustrated in Fig. 7. This change was characterized by a general constriction of all vascular elements. Most "true" capillaries were completely absent and the tissue was ischemic. The direct arteriolar-venular communications were open and became a dominant feature of the capillary network (Fig. 10). The arterioles were markedly constricted and many were closed. The arteriolar/venular diameter ratio tended to increase to 1:1. The circulating red cells formed large and rigid aggregates, which caused intermittent occlusion of the tips of the arterioles. The rate of blood flow was considerably decreased. Conjunctival tissue edema was usually present.

The whole sequence of changes from Vascular Pattern-Change II through

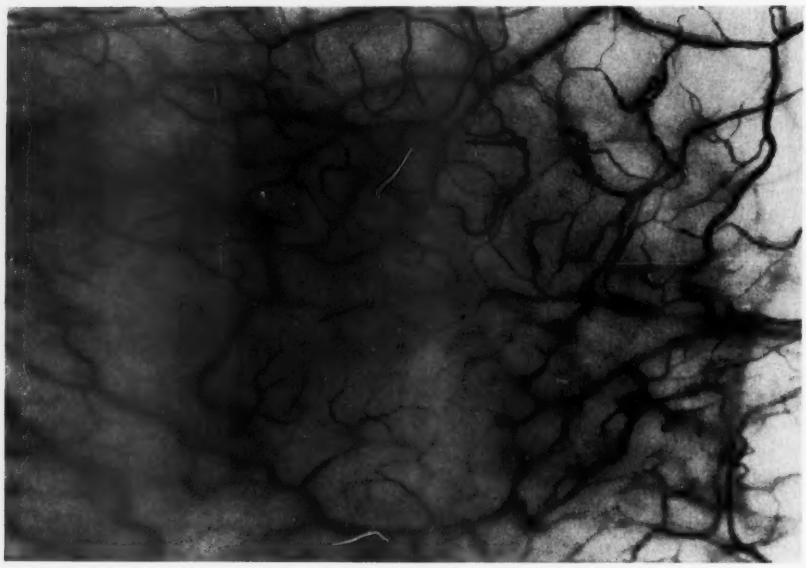

Fig. 9. The conjunctival vascular bed of a diabetic child (age 14 years, duration of diabetes 5 years) showing Vascular Pattern-Change I. Note the elongated and distended venules (v) with perivenular edema (e). 35 ×.

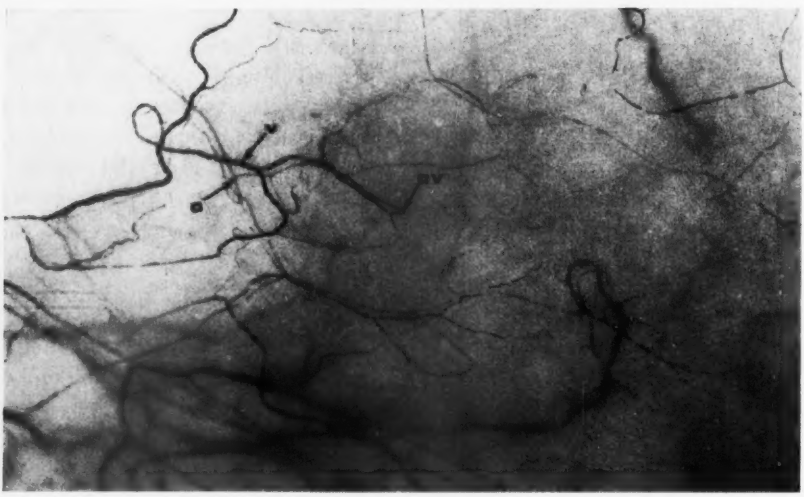

Fig. 10. The conjunctival vascular bed of a diabetic child (age 17 years, duration of diabetes 12 years) showing Vascular Pattern-Change II. Note the ischemia of the tissue and the open arterio-venous communications (av). Generalized aggregation of erythrocytes. 35 ×.

TABLE 3

The relationship between the type of vascular response and the duration of the diabetes.

Diabetic children		Vascular response		
Duration of diabetes	Number	Normal vascular pattern	Vascular pattern—Change I	Vascular pattern—Change II
0–4.9 yrs.	33	21	12	0
5–13 yrs.	37	13	21	3

Vascular Pattern-Change I to normal vascular pattern has occasionally been observed in young diabetics recovering from keto-acidosis and infection.

Of the diabetic children,[1] 33 (47 per cent) demonstrated Vascular Pattern-Change I and 3 showed Vascular Pattern-Change II. In 34 of the children (48 per cent) no functional changes were present justifying any separation from the pattern observed in the "control" children. However, in this last group, morphologic changes of irreversible nature might be present to such an extent as to suggest diabetes.

Table 3 shows the relationship between the type of vascular pattern and the duration of diabetes. The two groups of duration (0–4.9 years and 5–13 years) were chosen only to divide the total material available into equal numerical groups. It will be seen that Vascular Pattern-Change I occurred more frequently among the cases with longer duration, and the 3 cases showing Vascular Pattern-Change II were present only among the diabetics with a 5–13 years duration. A X^2 test showed that the relationship between the presence of abnormal vascular patterns and the duration of diabetes was statistically significant ($X^2 = 5.73$, $0.01 < p < 0.02$, D.F. = 2).

It was of interest that the two cases with longest duration of diabetes, i.e., 13 and 12 years which included the only case which showed diabetic retinopathy and evidence of nephropathy, were among the three cases showing Vascular Pattern-Change II.

No relationship was found between the type of vascular pattern and the age of the children or the insulin dose.

Analysis of Reversible Changes in the Conjunctival Vascular Bed

Venular Distension.—The most significant reversible change was a general distension of the venules (Fig. 8). At the same time the venules were often engorged, tortuous and showed localized bulgings of the walls

[1] No significant difference was found for the sexes.

TABLE 4

Distribution of the degree of distension of the venules, perivascular edema and intravascular erythrocyte aggregation.

	Number of cases	Distension of the venules (A:V ratio)				Perivascular edema (Grade)			Intravascular erythrocyte aggregation (Grade)				Intravascular erythrocyte aggregation, Total incidence
		1:2–1:3	1:4	1:5	>1:6	0	1	2	0	1	2	3	(per cent)
Diabetics	70	37	20	10	3	30	31	9	9	28	19	14	87
Controls	70	69	1	0	0	66	3	1	60	7	3	0	14

as fusiform dilatations. The venous end of the capillaries might have a funnel-shaped distension.

Table 4 shows the distribution of the degree of distension measured by the arteriolar/venular diameter ratio. Venular distension was encountered in 47 per cent of the diabetic cases varying quantitatively with a ratio from 1:4 to 1:7 and decreasing in frequency toward the lower ratios. There is a significant difference between its distribution among the diabetic children as opposed to the controls ($p < 0.01$).[1]

It may be of particular interest to note that, in the two cases which displayed the most advanced venular distension with an arteriolar/venular diameter ratio of 1:7, it was at the same time ophthalmoscopically demonstrated that the veins of the fundus were also greatly distended, tortuous and congested.

In Table 5 the degree of venular distension is correlated with the duration of the disease. Even if venular distension tended to occur more often in the cases of long duration, a X^2 test showed that this association was not significant.

Microscopic Perivascular Edema.—Table 4 gives the distribution of localized perivascular edema. It will be noted that this change is more frequent and marked among diabetic than among control children. This difference is significant ($p < 0.01$). When the venules displayed distension,

[1] Whenever the terms significant or statistically significant are used throughout the paper, the significance has been calculated from the standard error of the difference,

$$\sqrt{p \cdot q/n_1 + p \cdot q/n_2}.$$

If the difference between the two observed percentages is three or more times the standard error of the difference, the two groups have been considered significantly different ($p < 0.01$).

TABLE 5

Relationship of the degree of venular distension, perivascular edema and intravascular erythrocyte aggregation to the duration of the disease.

Duration of diabetes	Number of cases	Distension of the venules (A:V ratio)				Perivascular edema (Grade)			Intravascular erythrocyte aggregation (Grade)			
		1:2–1:3	1:4	1:5	>1:6	0	1	2	0	1	2	3
0–4.9 yrs.	33	21	9	2	1	14	16	3	3	16	9	5
5–13 yrs.	37	16	11	8	2	16	15	6	6	12	10	9

edema was most often present and more pronounced (Table 6). Microscopic edema, however, was not infrequent in cases with normal-appearing venules. A X^2 test demonstrated that there was a significant association between the distension of the vessels and the presence of microscopic edema ($X^2 = 15.35$, $p < 0.01$; D.F. = 1).

No association was found between the presence of perivascular edema and the duration of diabetes or insulin dose.

Intravascular Changes. Erythrocyte Aggregation.—In addition to the vascular changes, intravascular erythrocyte aggregation was often observed in the diabetic children. By careful examination the clumping was observed in all parts of the vascular peripheral bed. The more rigid and larger aggregates would cause intermittent plugging of the tips of the arterioles for a few seconds before they entered the capillaries. The aggregates were easily observed in the capillaries and those venules with the slowest rate of blood flow. Stagnation of the blood flow was occasionally observed and particularly so in cases showing venular distension.

In Table 4 the distribution of the degree of intravascular aggregation of the erythrocytes is given. Aggregation of the erythrocytes was found in 87

TABLE 6

Relationship between distension of the venules and perivascular edema.

	Perivascular changes (Grade)		
	0	1	2
Presence of distension of the venules	6	18	9
Absence of distension of the venules	24	13	0

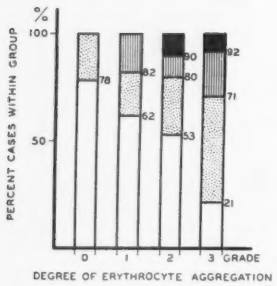

Fig. 11. The relationship between the degree of erythrocyte aggregation and the degree of venular distension. Degree of venular distension: A:V ratio 1:2–1:3 (blank area). A:V ratio 1:4 (strippled area). A:V ratio 1:5 (striped area). A:V ratio >1:6 (black area).

per cent of the diabetic compared with only 14 per cent among the control children. This difference is highly significant ($p < 0.01$).

In Table 5 the degree of erythrocyte aggregation is correlated with the duration of the disease. While there is a tendency for a more marked degree of aggregation to occur in cases with long duration, a X^2 test shows that this difference is not significant. The degree of the intravascular aggregation of the erythrocytes was correlated to the various significant findings in the vascular bed. In Fig. 11 the degree of intravascular erythrocyte aggregation is correlated to the degree of venular distension. It will be noted that the cases showing more marked degrees of aggregation are found also to exhibit increasing venular distension. The relationship was not absolute. Venular distension could be found in cases showing no aggregation, and in cases with marked arteriolar aggregation, no venular distension might be present. When the figures, which are indicated by the blank areas, are compared with the sum of the figures from the residual areas, a X^2 test shows that the association is just significant ($X^2 = 8.49$, $0.025 < p < 0.05$, D.F. = 3).

No further correlation between the single vascular changes and the degree of aggregation of the red cells was found.

No association was found between the degree of intravascular abnormalities and the age of the children or the insulin dose given.

Analysis of Irreversible Changes in the Conjunctival Vascular Bed

Arterioles.—Localized irregularities in the configuration of the arterioles were noted in only 2 cases (3 per cent), which is somewhat similar (8 per cent) to the finding in a group of young diabetics of 16–35 years of age, supporting the view that structural arteriolar changes, contrary to those of capillaries and venules, occur in a late stage of the disease (4).

Capillaries.—The capillary network generally appeared to be more irregular than that of the "healthy" children. In some places the capillaries

TABLE 7

Distribution of the degree of capillary elongation.

	Number of cases	Elongation of the capillaries (Grade)			
		0	1	2	3
Diabetics	70	17	26	19	8
Controls	70	65	5	0	0

might criss-cross and partly overlap each other, while in other places hardly any such vessels would show. When the individual capillaries were observed, the venous part displayed the abnormalities and the arterial part was generally unaffected. The changes in the venous part of the capillaries consisted of irregular elongation with angular tortuosities and configurative irregularities.

Although changes were noted in a high percentage of the diabetic children, considerable variations occurred as to the degree of involvement of the capillaries. In order to evaluate the tortuous capillary elongation, this was graded. (Grade 1 indicates that a few capillaries show elongated tortuosities; Grade 2 indicates that 10–50 per cent, and Grade 3 50–100 per cent, show this characteristic.) Such an estimate only allowed a rough grading of the visible changes and these did not necessarily parallel structural alterations which could not be observed by this technique.

The distribution of the estimated grading appears in Table 7. In the children used as controls, the changes were not only found in a small number of cases, but were also of a lesser degree than that of the diabetic children. The difference in distribution was statistically significant ($p < 0.01$).

In Table 8 the degree of capillary elongation is correlated to the duration

TABLE 8

The relationship between irreversible changes in the conjunctival vascular bed and the duration of diabetes.

Duration of diabetes	Number of cases	Elongation of the capillaries (Grade)				Perivascular "hyaline" infiltration
		0	1	2	3	
0–4.9 yrs.	33	9	14	10	1	1
5–13 yrs.	37	8	13	9	7	10

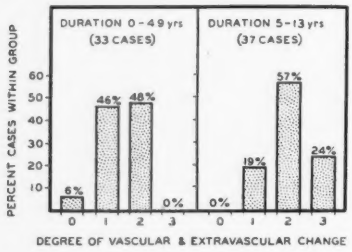

Fig. 12. The relationship between the irreversible changes in the conjunctival vascular bed and the duration of diabetes.

of the diabetes. Even though most of the cases which showed Grade 3 changes had long duration of diabetes, a X^2 test showed that the distribution of capillary changes was not significantly associated to the duration of the disease. Neither was there found a correlation between the degree of capillary change and the age of the children or the insulin dose.

"Hyaline" Infiltration of the Perivascular Tissue.—It appeared that if the edema, partly or completely, persisted, the originally edematous area became changed to pearly white and opaque or yellowish (8). "Hyaline" infiltration in the conjunctival tissue was found in 11 cases (16 per cent) among the diabetic children and not at all in the control group. This difference is highly significant ($p < 0.01$).

Table 8 shows the relationship between the degree of the perivascular tissue change and the duration of the disease. Ten of the 11 incidences of "hyaline" infiltration were found in children with diabetes of more than 5 years' duration.

Over-All Vascular and Extra-Vascular Findings.—As diabetic retinopathy is closely related to the duration of the disease, it would support the concept that, if a relationship between the morphologic conjunctival vascular changes and the duration of the disease could be demonstrated, then the changes in the conjunctival vessels might be related to the retinal vascular anomalies. In order to evaluate such a relationship, the irreversible vascular and extravascular findings were graded in stages of severity according to the scale previously used (5).

Fig. 12 shows the relationship between the over-all changes and the duration of the disease. More marked changes were found in the cases with long duration, and a X^2 test shows that the association is statistically significant ($X^2 = 13.66$, $p < 0.01$, D.F. = 2).

Discussion

The main object of the present investigation was to evaluate whether the irreversible changes in the conjunctival vascular bed progressed with

the duration of diabetes. In a previous study of adult diabetics no significant relationship between the duration of diabetes and the degree of vascular changes could be demonstrated (4). It was likely, however, that the aging changes on the vascular bed obscured the effect of diabetes because, in this evaluation, diabetics of various ages (16–75 years) were grouped together. Therefore, it appeared to be an advantage to repeat the study on diabetic children.

The present study demonstrates that a positive correlation exists between the changes in the conjunctiva and the duration of the disease. Since also there are apparent similarities between the conjunctival findings and certain of the retinal changes demonstrable clinically or patho-anatomically in the diabetics, it is likely that the changes are related and possibly produced by the same mechanism. The dissimilarities between the findings in the retina and the conjunctiva (i.e., presence and absence of capillary micro-aneurysms) may be due to differences in the architecture and functional need of the two vascular beds.

The most interesting finding in the diabetic children was the observation of various degrees of reversible alterations in the vascular bed. Approximately half of the diabetic children showed Vascular Pattern-Change I, characterized by various degrees of venular distension leading to a decreased rate of cell flow and increased permeability of the venular walls to plasma. A few children with long duration of diabetes demonstrated Vascular Pattern-Change II, characterized by arteriolar spasm and tissue ischemia. In the present study a significant association was found between the distension of the venules and the perivascular edema. Also, "hyaline" infiltration, the end result of prolonged edema, was correlated to the duration of the disease. Therefore, there appears to be a distinct association between the reversible response changes and the subsequent development of degeneration in the vascular bed. Direct evidence that the reversible conjunctival changes are precursory to the irreversible changes has been obtained by repeated microscopic observations in young diabetics (8).

The ophthalmoscopic retinal findings are not strictly comparable with those of the bulbar conjuctiva, due to the fact that the ophthalmoscope affords much less magnification than the device used in this study and the range of visibility covers only the larger vessels and does not extend to the very fine peripheral branches. Notwithstanding this difference, the vascular behavior, as viewed in the two ocular areas, appears to be due to common factors. The ophthalmoscope cannot disclose caliber changes of the terminal arterioles and smaller venules or intravascular erythrocyte aggregation, but does demonstrate the disturbances of the arterio-venous ratio in the young diabetics. Venous distension and engorgement in the retina of young

diabetics is a common finding and occur not only in the cases of retinopathy (3, 10, 12, 16) but also in cases without the initially-appearing small micro-aneurysms or punctate hemorrhages (1, 3, 17). So characteristic, even though not specific, is the finding of distended veins alone, that some authors regard this as the initial sign of retinopathy (11, 14). It is not unlikely that the long-term presence of venular distension with associated engorgement and slight exudation leads to hyalinization of the basement membrane of the retinal venules and capillaries and to venular-capillary micro-aneurysm formation in the inner nuclear layer of the retina (2).

The underlying cause of the abnormal vascular responses observed in the diabetics is at present under investigation.

Summary

1. An evaluation was made of the changes in the bulbar conjunctival vascular bed of 70 diabetics as compared to 70 non-diabetic children.

2. The changes found in the diabetic children differed quantitatively and qualitatively from those of the non-diabetic children.

3. The changes in the vascular bed of the diabetics consisted of irreversible degenerative changes and reversible vasomotor changes.

4. Increase of irreversible degenerative changes in the vascular bed was correlated with increased duration of diabetes.

5. The reversible changes were seen as various degrees of venular distension and arteriolar narrowing and formed a set of pathologic vasomotor responses designated Vascular Pattern-Change I and II.

6. The presence of abnormal vascular patterns became more frequent with increasing duration of diabetes.

7. Abnormal vascular patterns were associated with perivascular edema. "Hyaline" infiltration, the end result of prolonged edema, was correlated to the duration of the disease. Therefore, there appears to be a distinct association between the reversible response changes and the subsequent development of degeneration in the vascular bed.

La vascularisation de la conjonctive de l'œil chez les enfants diabétiques.

L'auteur a étudié les altérations de la vascularisation de la conjonctive de l'oeil chez 70 enfants diabétiques par rapport aux constatations faites chez 70 enfants non diabétiques. Les altérations relevées chez les enfants diabétiques par rapport aux enfants non diabétiques sont à la fois quantitatives et qualitatives. Les altérations vasculaires observées chez les enfants diabétiques consistent en phénomène de dégénérescence irréversibles et en troubles vasomoteurs réversibles. Le degré de gravité des altérations dégénératives augmente à mesure que le diabète est plus ancien. Les altérations vaso-motrices réversibles se présentent sous la forme de distensions des veinules et de rétrécissements des artérioles à des degrés divers et donnent un ensemble de manifestations vaso-motrices désignées sous le nom d'altérations vasculaires des types I et II. La présence de configurations vasculaires anormales se fit plus fréquente à mesure que le diabète était plus ancien. Ces configurations vasculaires s'accompagnèrent d'un œdème périvasculaire. On a constaté qu'il existe une relation

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Vitaminer och mineralämnen – viktiga tillväxtfaktorer för spädbarn

Ett spädbarn tredubblar sin vikt under första levnadsåret. Det är därför synnerligen betydelsefullt, att barnet under denna intensiva tillväxtperiod får en riktigt sammansatt kost, inte minst när det gäller vitaminer och mineralämnen.

Findus syn på vitaminproblemet

Vitaminbehovet kan tillgodoses på två olika sätt. Dels kan renframställda vitaminer ges i form av tabletter eller blandas in i kosten, dels kan man använda vitaminrika råvaror vid framställningen av barnmat. Genom att använda skonsamma behandlingsmetoder kan man ytterligare höja vitaminhalten på den färdiga barnmaten. Vad som här sagts om vitaminer gäller i lika hög grad mineralämnen.

Findus utnyttjar i första hand råvarans naturliga vitaminer. Först om dessa inte räcker till, tillsättes renframställda vitaminer. En sådan tillsats brukar kallas berikning. Principiellt bör en berikning ske på så

sätt, att huvudmängder av vitaminerna kommer från råvaran.

Vitaminer och mineralämnen i Findus barnmat*

Findus vällingpulver har en garanterad minimihalt av vitaminerna B_1, B_2 och Niacin samt av mineralämnena kalcium, fosfor och järn. I Findus Babyvälling och Findus Välling med mjölk garanteras också halten av vitamin C. C-vitaminhalten garanteras också i några andra Findus-produkter, nämligen Nyponsoppa, Nyponpuré och Svart Vinbärssaft. Samtliga dessa produkter är berikade. Beträffande vällingpulvren har man gått efter den principen, att barn, som får enbart Findus vällingprodukter, skall få sitt behov av de nämnda vitaminerna och mineralämnena helt tillgodosett. Vitamin A och D tillsättes ej vällingpulvren, eftersom medicinska fackmän anser, att dessa vitaminer lämpligen ges i form av A-D-vitamindroppar eller liknande preparat. — Findus övriga barnmatsprodukter innehåller enbart naturliga vitaminer och mineralämnen.

Kontroll av C-vitaminhalten.

Eget vitaminlaboratorium

För att kunna kontrollera vitaminhalten i alla dessa produkter har Findus ett särskilt vitaminlaboratorium, där vitaminerna B_1, B_2 och C bestämmes kvantitativt på de färdiga produkterna. Framför allt C-vitaminanalyserna har blivit en viktig metod för att bestämma, hur skonsamma konserveringsmetoderna är. Ju mera C-vitamin, som finns i de färdiga produkterna, desto bättre är konserveringsmetoden. Vitaminanalyserna har därför icke blivit ett självändamål utan användes, i likhet med kvantitativa bestämningar av enzymaktivitet, som ett medel att utveckla allt bättre konserveringsmetoder.

Analystabeller för barnmat

För att få en helt utomstående kontroll av barnmatens sammansättning analyserar Statens Institut för Folkhälsan Findus alla barnmatsprodukter med avseende på protein, fett, kolhydrat, etc., vitaminerna B^1, B^2, Niacin och C samt mineralämnena kalcium, fosfor och järn. Analysresultaten sammanställes i en tabell, som sändes till landets samtliga läkare och barnavårdscentraler.

*) Den som har intresse av att närmare granska halten av dessa näringsämnen i Findus barnmat kan genom rekvisition från AB Findus, Bjuv, erhålla den analystabell som sändes till landets samtliga läkare och barnavårdscentraler (se ovan).

Dessa fakta är sammanställda av chefen för Findus forskningslaboratorium, docent Carl Erik Danielson.

Tuber om 20, 50 och 100 g
Burk om 1000 g

PHARMACIA

entre l'infiltration "hyaline" – qui constitue l'aboutissement final d'un œdème prolongé – et l'ancienneté de la maladie. Il semble donc qu'il y ait un rapport étroit entre le caractère de réversibilité des modifications pathologiques et l'évolution ultérieure de la dégénérescence vasculaire.

Das Gefässbett der bulbären Bindehaut bei diabetischen Kindern.

Eine Auswertung der Veränderungen in dem Gefässbett der bulbären Bindehaut bei 70 diabetischen Kindern wurde durchgeführt und mit 70 nicht diabetischen Kindern verglichen. Die bei diabetischen Kindern gefundenen Veränderungen wichen in quantitativer als auch qualitativer Beziehung von denen der nicht diabetischen Kinder ab. Die Veränderungen im Gefässbett von Diabetikern bestanden aus nicht umkehrbaren degenerativen und umkehrbaren vasomotorischen Änderungen. Die Zunahme von nicht umkehrbaren degenerativen Veränderungen im Gefässbett stand zu einer längeren Dauer des Diabetes in direkter Beziehung. Die reversiblen Veränderungen bestanden aus verschiedenen Graden von venöser Ausdehnung und arterieller Verengerung und bildeten einen Satz von pathologischen vasomotirischen Reaktionen, welche als Gefässmusteränderungen I und II bezeichnet wurden. Die Anwesenheit abnormaler Gefässmuster wurde mit zunehmender Dauer des Diabetes häufiger. Abnormale Gefässbilder waren mit perivaskulärem Oedem verbunden. Hyaline Infiltration als Endergebnis von langdauerndem Oedem stand zur Dauer des Diabetes in Wechselbeziehung. Es scheint daher, dass eine deutliche Verbindung zwischen den reversiblen Reaktionsänderungen und der nachfolgenden Entwicklung von Degeneration im Gefässbett besteht.

El fondo vascular conjuntivobulbar diabético infantil.

Estableciόse una evaluación de los cambios en el fondo vascular conjuntivobulbar de 70 niños diabéticos comparados con 70 no diabéticos. Los cambios revelados en los niños diabéticos se diferenciaron cuantitativa y cualitativamente de los niños no diabéticos. Los cambios en el fondo vascular de los diabéticos consistió en cambios degenerativos irreversibles y en cambios vasomotores reversibles. El aumento de los cambios degenerativos irreversibles en el fondo vascular estuvo correlacionado con el aumento de la duración de la diabetes. Los cambios reversibles aparecieron como varios grados de distensión venular y estenosis arteriolar formando un conjunto de respuestas vasomotoras patológicas designadas con la denominación de: Cambios I y II de la silueta vascular. La presencia de siluetas vasculares anormales se hizo más frecuente a medida que aumentara la duración de la diabetes. Las siluetas vasculares anormales estuvieron asociadas con edema perivascular. La infiltración de "hialina", último resultado del edema prolongado, estuvo correlacionada con la duración de la enfermedad. Por consiguiente, aparece que existe una asociación distintiva entre los cambios responso reversibles y el subsiguiente desarrollo de la degeneración en el fondo vascular.

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A Case of Congenital Friedreich's Disease, with Autopsy

by ERNA CHRISTENSEN and J. EGHOLT RASMUSSEN

Friedreich's disease belongs to the heredo-degenerative group of ataxia also including Marie's cerebellar ataxia and mixed forms. Ford states, that we have three components in Friedreich's disease, cerebellar ataxia, posterior column ataxia and pyramidal tract signs.

In his monograph of the heredo-ataxies Sjögren classifies the patients in four clinical groups. Schut & Haymarker also divide their material in four groups from a pathological point of view. Hassin states that Friedreich's and Marie's ataxia are different morbid conditions, the one is a disease of certain tracts of nerve fibres, and the other of certain groups of cells. In Friedreich's ataxia the degeneration in the posterior columns is primary. Spillane, Eckel & Winkelman and Krücke state that a distinction between the different forms of ataxia is artificial, because of the many mixed forms.

Most authors regard the heredo-ataxic diseases as belonging to the abiotrophic neurological diseases, but Russell states that we here are dealing with a toxic degeneration.

The classical ataxia is for the first time described by Friedreich in 1863 as a familial hereditary disease appearing in childhood, fully developed at the age of fourteen and slowly progressing until death.

The classical symptoms are static locomotoric ataxia, absence of tendon reflexes on the legs, skeletal anomalies, excavated feet, often pyramidal symptoms, muscular atrophies and disturbances in the sensation. Among other symptoms atrophy of the optic nerves and dementia can also be found.

Some patients have vegetative symptoms and disturbances in the heart-rhythm and respiration. Sudden death can be seen caused by acute heart-dilatation (Philippe & Oberthur, Guillain & Mollaret, Ellwood and Eckel & Winkelman).

A. and L. van Bogaert found abnormal electrocardiogram in a material of eight patients with Friedreich's ataxia between 7–35 years of age with symptoms from infancy. There was no information of intoxication, endo- or myocarditis in these cases, and the authors concluded, that the electro-cardiogram findings pointed at an intramyocardial electrogenesis.

The pathological-anatomical findings in the classical Friedreich's ataxia are characterized by a thin spinal cord due to atrophy or hypoplasia (micromylia) (Bielshowsky

and Hallervorden). Transverse sections of the cord reveal atrophy of the posterior columns and posterior roots (Ule).

Histological examination shows marked, but not complete, myelin degeneration in the column of Burdach and Goll. In cases combined with clinical cerebellar and pyramidal symptoms, there is also degeneration of nerve-cells in cerebellum and myelin degeneration in the spino-cerebellar and pyramidal tracts. Clark's column can be affected in some cases, and in some patients who have had anomalies in respiration and heart action, degeneration in the nuclei of n. vagus and in tractus solitarius can be seen (Philippe & Oberthur), while in other of these patients no degeneration can be found, but histological significant chronical myocarditis (Russell).

In the literature we have found no case of congenital Friedreich's ataxia with death at the age of six months.

Case Report

Case record no 3817/56 Children's Department, Centralsygehuset, Randers.

Boy born 12.1. 1956. In hospital from 13.6. 1956 until death 25.6. 1956. *Family history:* No disposition to nervous diseases in the family, the parents are not related and both are in good health. *Siblings:* Number two of two, his older sister died 6 months old at home with symptoms similar to our patient. *Pregnancy:* had been quite normal. Birth without complications. Birth-weight 3600 g, length 51 cm, crying normally, no cyanosis or weakness were observed. *Early development:* Mother-milk for four months, A–D vitamins in sufficient doses. Atonic since birth. Gaining normally in weight. No intercurrent diseases. *Present disease:* The day before admission to hospital he was examined in the out-patient clinic because of increasing dyspnoea and universal atony.

Examination.—Psychical bright, prattling, following the examiner interested with his eyes. Physical: Universal hypotonia and muscular weakness, he was able to rise his head for a short moment, but unable to sit up, moving arms and legs with poor strength. He was dyspnoeic, but without cyanosis. Thorax was very narrow, the musculature atonic and the subcutis abundant but loose, both the cutan and tendon reflexes were missing. Besides this the examination did not show anything of interest.

The case was diagnosed as amyotonia congenita and—*ut aliquid fiat*—Ephynal medicamentation was prescribed.

The following night he was admitted to the children's department for febrilia. At that time he was pale, atonic, in very bad universal condition. He was short-breathing, groaning. The eyes were turned upwards, the pupils asymmetrical. The eyegrounds were pale, the retinal vessels normal, but small pigmented spots could be seen in the eye-ground. Otological examination revealed nothing abnormal. No neck- and back-stiffness. Stetoscopical examination of lungs and heart did not show anything abnormal.

X-ray of thorax revealed a normal heart, but dense structure of the lungs at both sides of the heart and especially dense structure in the right apical region. X-ray-diagnosis: Right-sided pneumonia.

Laboratory examinations.—The spinal fluid was clear, the intraspinal pressure normal, and both cells and protein content were normal. Urine normal besides positive sugar reaction once, blood-sugar 107 mg %, hemoglobin 69 %, white blood cells 9870, differential count at normal levels. Moro test negative.

Course and treatment.—Oxygen-inhalation was instituted and 100 mg Achromycin

was given twice a day. He improved during this treatment, but the temperature was still elevated and the respiration insufficient with egal excursions. Sometimes he grimaced, and the eye-movements were incontrolled, now and then with squinting.

Two days before death he had left-sided tonic and clonic convulsions which was stopped with sol. chlorali-hydratis. Oxygen-inhalation, energical antibiotic treatment and tracheal suction were continued, but he died in hyperthermia 12 days after admission.

Clinical Summary

A six months old boy had since birth been increasingly atonic and weak and the last fourteen days of his life he became dyspnoeic. Twelve days before death a right-sided pneumonia developed, it was cured with antibiotics. Two days before death there was a sudden respiration-stop and left-sided convulsions. After this attaque his condition was very poor until death.

Autopsy (J. V. Thorborg, M.D. Pathological Institute, Centralsygehuset, Randers):

Weight 7.5 kg, length 70 cm, well-shaped child, abundant subcutaneous fat tissue. Post mortem examination revealed only abnormalities in the lungs besides the central nervous system. Both lungs were atelectatic especially the right upper and central lobe, and disseminated bronchopneumonic foci were found. Histological diagnosis: Atelectasis et hyperemia pulmonum. Bronchopneumoniae bilaterales in primi pulmonis dx. The heart was macroscopical normal, but histological examination was not carried out. Histological examination of the psoas muscle revealed unspecific inflammation, probably a terminal phenomenon.

Brain autopsy

Macroscopical examination of the central nervous system: Brain weight after formaline fixation 850 g. The brain surface and the vessels did not reveal any changes. Coronal sections showed normal ventricles and macroscopically normal brain tissue, Also mesencephalon, pons, medulla oblongata, cerebellum and the spinal cord looked normal at macroscopical examination both on the surface and on numerous horizontal sections.

Histological examination of the central nervous system: Sections were taken from several parts of the cortical grey matter, the basal ganglia, mesencephalon, pons, cerebellum, medulla oblongata, and from both the cervical, thoracal and lumbar part of the spinal cord. All sections were embedded in paraffin and stained with hematoxylin-eosin, v. Gieson Hansen's stain, Mallory's anilin-blue-orange-G, Davenport's axis-cylinder-stain and Mahon's myelin-stain.

Cortex.—The nerve-cells are not quite maturated, but besides degeneration—as found after hypoxia or anoxia—can be seen. The nuclei are pycnotic, the cytoplasm is swollen or pale and shrinken, and there is pericellular edema and hyperemia. The white matter shows only partly myelinisation, hyperemia and edema, but no glial proliferation or degeneration. In the periventricular tissue small fresh perivascular hemorrhages can be seen. The ependymal cells on the ventricular walls are normal in most places, but somewhere they are missing and here glial proliferation can be seen.

The basal ganglia contains normal or slight edematous nerve cells and normally myelinated white substance.

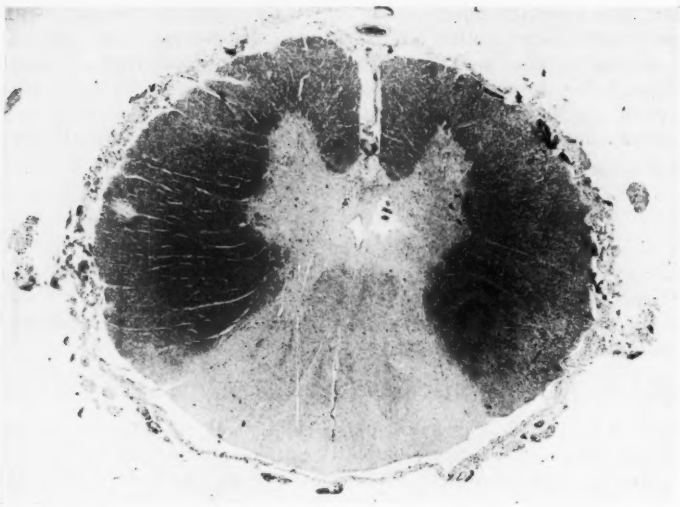

Fig. 1. Cervical spinal cord with lack of myelinisation in the posterior tracts and roots. Mahon's myelin stain. (10 ×.)

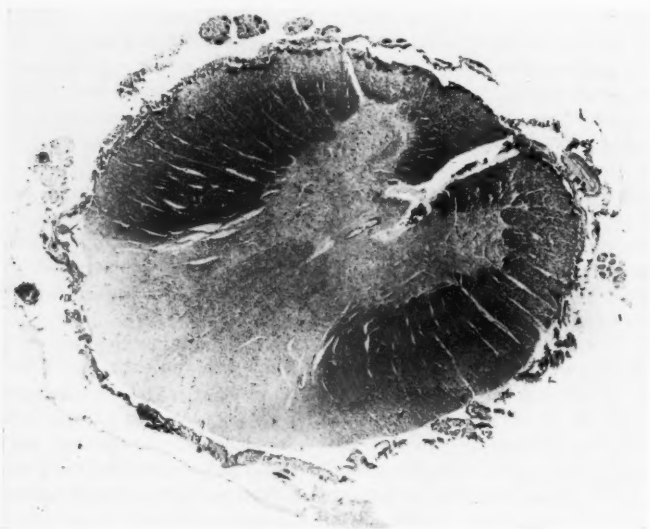

Fig. 2. Thoracal spinal cord with lack of myelinisation in the posterior tracts and roots. Mahon's myelin stain. (10 ×.)

Mesencephalon and pons have normal or slightly swollen nerve cells. The myelinisation in the white substance is normal except in lemnisci mediales, where it is very weak. No glial proliferation can be seen. The myelinisation in the cerebral peduncles and pyramidal tracts are quite normal.

Medulla oblongata,—The myelinisation in lemnisci mediales is totally missing, and the nerve cells in nucleus cuneatus and gracilis and n. vagi are degenerated with pycnotic nuclei and pale shrunken cytoplasm, but without any glial proliferation. The nerve cells in all the other brain-nerve nuclei are normal.

Cerebellum.—The fetal stratum granulosum cell layer on the surface is preserved. Both the Purkinje cells and the nerve cells in the different nuclei and the white matter are fully developed and quite normal.

Medulla spinalis.—All sections from the spinal cord reveal identical changes, as the myelinisation is completely missing in tractus gracilis, partly missing in tractus cuneatus on both sides in the dorsal tracts. In the anterior tracts and the side tracts the myelinisation is quite normal. The grey substance is normal except for slight degeneration of some of the anterior horn cells. Nowhere glial proliferation or inflammatory changes can be seen. The myelinisation in the posterior roots are delayed compared with the anterior roots.

Discussion

From the fragmentary survey of the literature it can be seen that Friedreich's ataxia most often is hereditary, fully developed about the age of fourteen and slowly progressing. The typical pathological findings are myelin-degeneration and slight glial proliferation in the posterior roots. Degeneration of the nerve cells in the nuclei of n. vagus can be seen in some of the patients who have had myocardial affection and difficulties in respiration, while histological examination of the heart in others reveals myocarditis.

About our patient the only indication of hereditary disease is the fact that his older sister died at home at the same age with similar symptoms, but here no autopsy was carried out. The pregnancy has been normal. The disease in our patient is congenital with vigorous aggravation the last fourteen days of life, and as he first was admitted in hospital at this time the clinical picture is difficult to clear up, but he is evidently atonic and dyspnoic before and after his right-sided pneumonia.

The histological picture with degeneration of the nerve cells in nucleus n. vagi, nucleus gracilis and cuneatus, the deficiency of myelinisation in lemniscus medialis, in tractus gracilis and cuneatus can explain the clinical symptoms; difficulties in respiration, weakness and universal atony. The convulsions two days before death have possibly been of anoxic origin, even if we do not find a real explanation of the phenomenon. His disturbances in breathing and heart-action are considered to be of central origin as other authors have proved.

Unfortunately the heart muslces have not been histologically examined, and therefore we cannot quite exclude a myocarditis, but the degeneration in the vagal nuclei can explain his difficulty in respiration.

Pathogenesis. Longworthy states that the myelinisation in tractus gracilis, cuneatus and lemniscus medialis takes place from the 28th fetal week and is complete at the end of the second year of life, but the thickness of the myelin sheats are increasing until the age of fourteen. In our patient, dying at the end of 6 months there was nearly complete lack of myelinisation in these tracts and no signs of myelin destruction or glial proliferation. Therefore a degeneration is considered unlikely, the deficiency of myelinisation in the posterior columns primary and the degeneration of the nerve cells secondary.

It is possible that some of the patients in Brandt's material with Oppenheim's amyotonia congenita and Krabbe's patient with congenital muscular aplasia have had a delayed myelinisation, as those patients were atonic from birth, retarded in static development with unsteady gait, hypotonia, lowered power and weak tendon reflexes. Some of them recovered during childhood, but others had their symptoms during their entire life. Autopsy has not been performed in these cases.

The etiology is obscure, but in veterinary medicine a trembling disease among baby pigs is well-known. Histological examination of spinal cords in such cases reveals an incomplete development of myelin sheats in the spino-cerebellar tracts. This disease is considered to be due to incorrect feedings of sows and gilts during the gestation period. The pigs do not die from the disease and the symptoms disappear after some time, and histological examination of cured pigs shows normal myelinisation in the spinal cord. Therefore it is not a mal-development but retardation of myelinisation (E. Christensen & N. O. Christensen).

Nothing can be proved about the etiology of the abnormal myelinisation in the spinal cord in our patient, but it is not a usual case of Friedreich's disease. It is a sort of congenital dysplasia, and even if the trembling disease in new born pigs is not identical with the disease in our patient the comparison opens new perspectives for future examinations and studies.

Summary

A six month old boy who has been weak and atonic since birth died with increasing dyspnoe. Autopsy revealed lack of myelinisation in the posterior column of the spinal cord and the posterior roots. Histological examination did not show signs of degeneration and the abnormal myelinisation is considered being a mal-development.

Description d'un cas congénital de maladie de Friedreich avec les resultats de l'autopsie.

Un bébé du sexe masculin qui présentait de l'asthénie et de l'atonie depuis sa naissance est mort à l'âge de six mois après avoir souffert de dyspnée de plus en plus marquée. L'autopsie a révélé l'absence de myélinisation du cordon postérieur de la moelle épinière et des racines rachidiennes postérieures. L'examen histologique n'a fait apparaître aucun signe de dégénérescence et l'on pense que cette myélinisation anormale est à considérer comme une malformation.

Ein Fall von kongenitaler Friedreichscher Krankheit mit Autopsiebefund.

Ein 6 Monate alter Knabe, der von Geburt an schwach und atonisch war, starb mit Erscheinungen von zunehmender Dyspnoe. Die Autopsie enthüllte mangelnde Markentwicklung in der hinteren Rückenmarksäule und den hinteren Wurzeln. Die histologische Untersuchung zeigte keine Anzeichen von Degeneration und die abnormale Entwicklung der markhaltigen Substanz wird als eine Missbildung aufgefasst.

Un caso de enfermedad congénita de Friedreich y autopsia.

Un niño de seis meses de edad, débil y atónico desde el nacimiento, murió con disnea creciente. La autopsia reveló falta de mielinización en la columna posterior del cordón espinal y raíces posteriores. El examen histológico no mostró señales de degeneración y la mielinización anormal se considera como un mal desarrollo.

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An Epidemic Among Swedish Children Caused by Adenovirus Type 3

By LARS KJELLÉN, BO ZETTERBERG and ARNE SVEDMYR

An epidemic of "pharyngoconjunctival fever" apparently caused by adenovirus type 3 was described in great detail by Bell and co-workers in 1955 (1). The clinical syndrome hinted at by this name seemed to be rather typical. When an epidemic of a similar disease occurred in Sweden during the late summer of 1955 it was accordingly studied in some detail. Clinical and epidemiological observations as well as the correlation to prevalent infections with adenovirus type 3 will be described in this paper.

Aetiological observations

The present investigation was started in the middle of August 1955, about one month after the occurrence of the first known cases with the symptoms typical for this epidemic: upper respiratory disease, conjunctivitis and diarrhea. The local medical authorities in the two neighbouring communities concerned (the town of Kumla, 9600 inhabitants; the municipality of Frövi, 2600 inhabitants) by this time knew of at least a hundred cases, predominantly among children. One of us (Z.) therefore visited the epidemic area and personally investigated some of the cases with acute disease or in convalescence. Anamnestic and epidemiological data were collected. Stools and paired sera were obtained from 25 patients and 3 healthy family contacts (parents of sick children); conjunctival swabs from 8 cases. Samples of sewage were taken from the two localities, one of them from the main collection tank, the other at the outlet into the lake "Väringen", 150 m from a municipal swimming place. New specimens of stools and blood were taken about two months later. From 11 of the patients a third blood specimen was drawn 6 months after the first one.

The specimens were tested according to methods outlined elsewhere (2). Adenovirus type 3 was recovered from 23 of the 25 primary stool specimens obtained from persons who were or had been ill. Three of these positive specimens were actually taken about a month after onset of disease. Two persons still had the virus in their second specimens taken two months after the disease. The virus content of two of the primary stool speci-

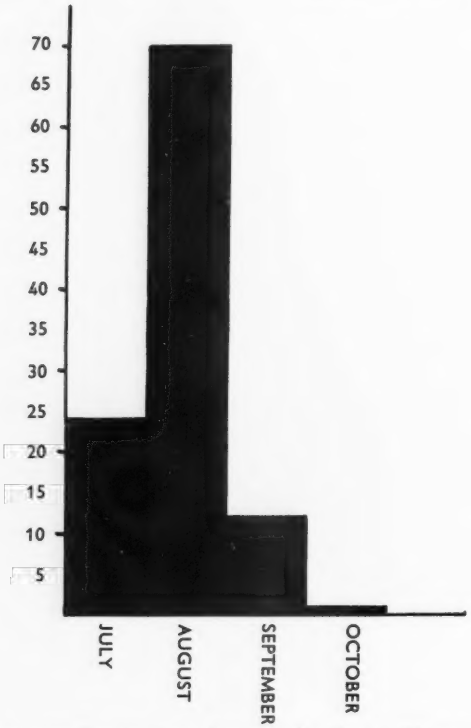


Fig. 1. Distribution, according to time of onset, of patients with some typical symptoms (virus-positive cases included).

mens, taken 6 and 9 days after onset of disease, was titrated out. Titers of $10^{-6.8}$ and $10^{-7.1}$ per g of stools were obtained.

The three healthy contacts were all shown to excrete type 3 virus. Such virus was also found in 2 of the 8 conjunctival swabs and, in low concentration, in both samples of sewage water. Neutralizing antibodies were demonstrated in the convalescent sera of all virus-positive cases tested. Rising titers were found in the second blood sample of patients who were acutely ill when the first specimen was drawn. Titers of complement fixing antibodies showed a similar pattern. Furthermore, there was a significant drop in CF titer in 9 of the 11 specimens taken half a year later.

The data summarized above indicate that the persons investigated were infected with adenovirus type 3 at the time of their symptoms. The presence of measureable amounts of virus in the sewage water suggests, furthermore, that such infections were widely spread in both communities at the height of the epidemic.

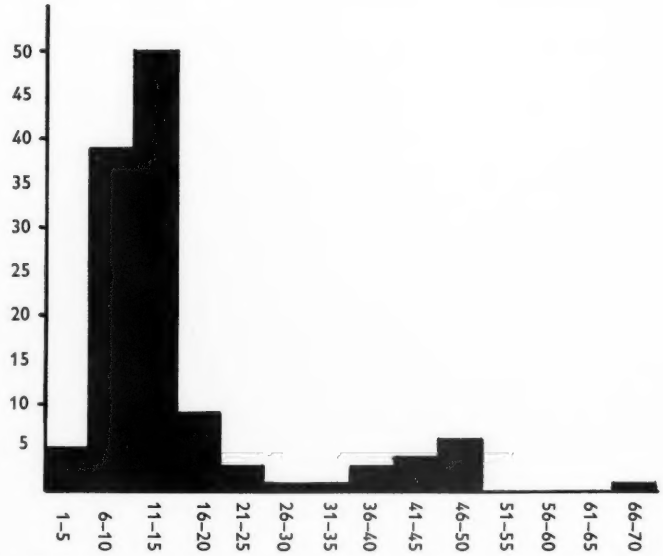


Fig. 2. Age distribution of patients with some typical symptoms (virus-positive cases included).

In order to confirm that there was a real correlation between the infections with adenovirus type 3 and the epidemic disease the frequency of such infections among persons who had shown signs of the epidemic disease had to be compared with that among healthy persons. A second visit was therefore made to Kumla in October, i.e. about two months after the height of the epidemic. At this time serum specimens were collected from large groups of persons who were also carefully questioned for signs of disease during the preceding months. Similar specimens were in addition collected from healthy persons in the neighbouring community of Hallsberg (5200 inhabitants) where apparently very few cases suggestive of pharyngoconjunctival fever had occurred this year. Sera and anamnestic data were thus obtained from 102 persons who had shown symptoms compatible with pharyngoconjunctival fever (in addition to the 23 patients studied previously), from 81 family contacts without symptoms, 101 healthy adults working at a factory in Kumla, 111 healthy school children in Kumla, 56 healthy school children in Hallsberg and 75 healthy adults working at a factory in Hallsberg.

The distribution according to time of onset and age of patient among the cases with symptoms are shown in Figs. 1 and 2. Although the material does not represent a mean of the population in Kumla and Frövi, it seems

TABLE 1.

Frequency of antibodies in various population groups of the epidemic area as well as in a neighbouring community.

Population group	Neutralizing antibodies against type 3 adenovirus		Complement-fixing antibodies against adenovirus		
	Number of persons tested	Per cent pos. (titer ≥ 2)	Number of persons tested	Per cent with a titer of ≥ 8	Per cent neg. (titer < 2)
Patients with symptoms . .	120	93	124	80	9
Family contacts without symptoms	81	81	81	49	17
Healthy adults in Kumla . .	98	81	101	11	37
Healthy children from schools in Kumla	109	77	111	36	18
Healthy adults from Hallsberg	75	79	74	30	31
Healthy children from schools in Hallsberg	56	57	56	32	21

evident that the epidemic reached its peak in August and that it predominantly involved children.

The frequencies of neutralizing and complement fixing antibodies among the various population groups tested are shown in Table 1. The fact that only 93% of the group with symptoms had neutralizing antibodies indicates that some of the cases had actually not been infected with type 3 virus. On the other hand, the frequency of neutralizing antibodies was significantly higher in this group than in any of the others. The CF antibodies which should be more representative for a recent infection were much less common in the various control groups than among the persons who had been ill.

These results confirm the correlation between infections with adenovirus type 3 and the epidemic disease. The discrepancy, within the control groups, between the high figures for neutralizing antibodies and the considerably lower ones for CF antibodies suggests that exposure to type 3 virus prior to the epidemic was common.

Clinical Observations

The frequency of various symptoms among the patients known to excrete adenovirus type 3 is shown in Table 2. The anamnestic data of the larger group in the table may be expected to be less reliable as they were not collected until two months after the peak of the epidemic. However, the distribution of symptoms within this group was similar to that of the virus-

TABLE 2.

Frequency of various symptoms (in per cent).

Patients	Total number of cases	Fever	Headache	Conjunctivitis	Rhinitis	Pharyngitis	Nausea	Vomiting	Stomach-ache	Diarrhea
Cases verified by the isolation of adenovirus type 3	23	87	74	48	30	91	48	26	52	35
Other cases with some "typical" symptoms during the epidemic	102	81	74	65	55	55	51	40	43	37

positive cases. The higher frequency of pharyngitis among the virus-positive cases may be due simply to the fact that this symptom was the basis for selection of most of these cases.

With the exception of the gastrointestinal symptoms the pattern approaches that previously described in great detail by Bell and co-workers (1) which was summarized in the name suggested for the syndrome: "pharyngo-conjunctival fever". However, these authors encountered nausea, vomiting or diarrhea only in a few cases. On the contrary, about half of our patients had gastrointestinal symptoms. It should be mentioned in this connection that bacteriological investigation of the 26 virus-positive stool specimens was negative for Salmonella and Shigella bacteria. A double infection with adenovirus and a bacterial pathogen in so many cases seems therefore most improbable.

Although the combination of symptoms varied for the individual patients, a "typical" picture of a severe case can be shortly outlined. The onset of disease was usually acute with high fever (39–40°C), lassitude, severe headache, sore throat (usually mild), conjunctivitis and rhinitis. Two to four days after onset the patient experienced nausea and vomiting, often together with stomach-ache and diarrhea. The fever remained at a high level usually for 5–7 days. The headache was of a shooting character and sometimes severe enough to seem suggestive of a meningitis. The conjunctivitis and rhinitis were quite mild in most cases and not always accompanied by a discharge. Both eyes were usually affected. The gastrointestinal symptoms were, in most cases, not very severe. In a few cases, however, they simulated an acute abdomen. The diarrhea, when present, lasted for only one or two days. A few patients complained of pains in the neck and back.

In severe cases the patients were deeply affected by the disease and certainly more than could be solely attributed to the fever. In such cases the convalescence lasted up to three weeks.

Epidemiological Considerations

In their study (1) Bell and co-workers suspected that, beside person-to-person spread, swimming pools might be a common source of infection during an epidemic of pharyngoconjunctival fever. A similar possibility for spread was obvious in the present epidemic which occurred in summer time before the schools started. A high proportion of the inhabitants of the two communities involved (74% of the Kumla cases) thus admitted to have been swimming in either of two small lakes. One of them, lake Väringen at Frövi, was also the recipient of sewage which was shown to be contaminated with adenovirus type 3. The outlet was located 150 m from the swimming place. The other lake, at Kumla, was a small artificial lake without known contamination with sewage.

The statement of Bell and co-workers (1) that "the period of communicability as indicated by presence of virus decreases from 100% during the first few days of illness to practically nil after the ninth day of illness" was apparently made without adequate studies on the excretion of virus in stools and was based principally on the occurrence of virus in specimens taken from pharynx or conjunctiva. Our results demonstrate that the concentration of virus found in the stools may be comparable to that found in infections with so-called enteric viruses like polioviruses, Coxsackie and ECHO viruses and that the excretion may also last for months. The possibilities for spread should thus be the same as for the other enteric viruses. The prevalence of gastrointestinal symptoms in the Swedish epidemic suggests, however, that the virus involved was more enterotropic than the strain encountered by Bell and co-workers (1). If so, a discrepancy in the fecal excretion of virus seems conceivable. It is noteworthy, furthermore, that the three healthy family contacts (all parents of sick children) studied by us were also found to excrete virus in their stools. It is possible, however, that minor symptoms may have been overlooked by these persons. In the American study there was a 100% correlation between the presence of virus and symptoms.

Summary

An epidemic of "pharyngoconjunctival fever" which occurred in the middle of Sweden in the summer of 1955 is described. A correlation to infections with adenovirus type 3 was found.

penicillin som profylaktikum

Infektion orsakad av penicillinkänsliga mikroorganismer kan förebyggas av penicillin, givet i relativt liten dos. Värdet av penicillinprofylax är framför allt visad vid reumatisk feber. Förhindras utbrottet av en hemol. streptokockinfektion är risken för att patienten skall få reumatisk feberattack mycket liten. Varje patient, som haft reumatisk feber, bör därför enligt American Heart Association's och WHO's rekommendationer behandlas profylaktiskt med penicillin. Profylaktisk behandling ges antingen parenteralt med långverkande penicillin eller med penicillin dagligen per os. Inom en familj, skola eller mindre sluten enhet, där fall av halsfluss eller scarlatina inträffat, kan ytterligare utbrott av H. S.-infektion förebyggas om penicillin ges profylaktiskt till var och en, som utsatts för smitta.

Behandling:

1. Kontinuerlig profylax för att förebygga recidiv av reumatisk feber:
   Per os—Permapen 100.000—200.000 IE 2 ggr dagligen, tabletter eller mixtur.
2. Behandling av hemol. streptokockinfektion, såsom halsfluss och scarlatina:
   Per os—Permapen 200.000 IE 3—5 ggr dagligen i 10 dagar, tabletter eller mixtur
   Intramuskulärt—Permapen comp.
   1 injektion var 3—4:e dag.

Permapen

mixtur, med persikosmak:
Glas à 60 ml, innehållande 60.000 IE DBED-penicillin per ml. 1 tesked=300.000 IE.

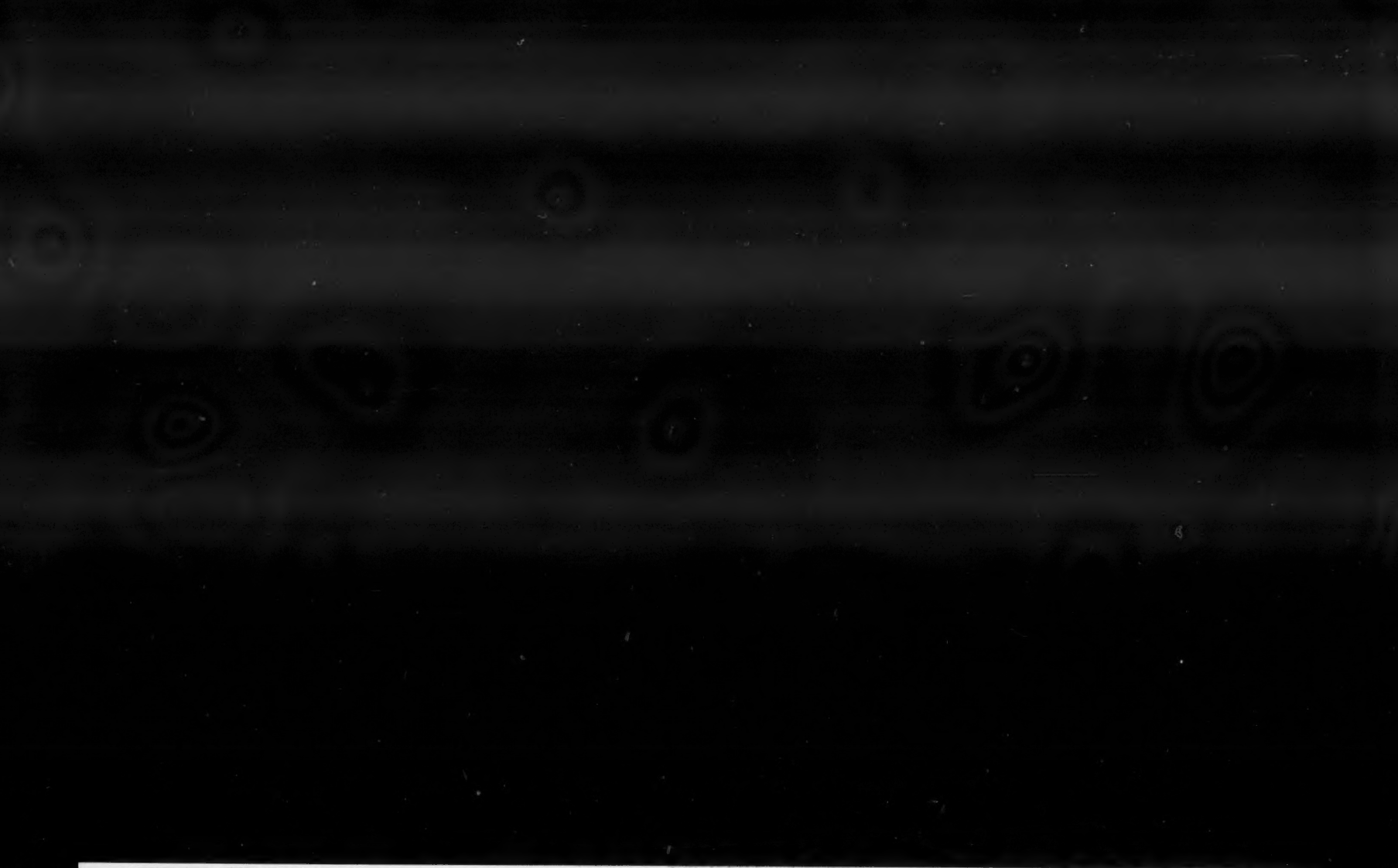
tabletter: Förpackningar om 18 och 30 tabletter.
Varje tablett innehåller 200.000 IE DBED-penicillin (benzatinpenicillin)

Permapen comp.

Ampull à 600.000 IE (100.000 IE bensylpenicillinkalium, 200.000 IE DBED-penicillin och 300.000 IE bensylpenicillinprokain)

Pfizer

PFIZER AKTIEBOLAG
STOCKHOLM 5



This type of virus was thus isolated from the stools of 23 out of 25 patients with "typical" symptoms and in addition also from the stools of three apparently healthy family contacts. The titer of fecal virus was high and some cases excreted the virus in their stools for at least two months. Virus was recovered from the sewage water of both communities involved in the epidemic. A serological study performed after the epidemic on a larger group of persons confirmed the aetiological correlation of adenovirus type 3 to the epidemic disease. The frequencies of symptoms were similar to those found by Bell and co-workers (1) with the notable exception that gastrointestinal symptoms like nausea, vomiting, stomach-ache and diarrhea were encountered in not less than about half of the Swedish cases. Some epidemiological data are discussed and compared with those collected by Bell and co-workers (1).

Épidémie à adénovirus du type 3 chez des enfants suédois.

L'auteur donne la description d'une épidémie de « fièvre pharyngo-conjonctivale » survenue dans les régions du centre de la Suède au cours de l'été de 1955. Cette épidémie était en relation avec des infections à adénovirus du type 3. Des virus de ce type ont été retrouvé dans les selles de 23 malades sur 25 qui présentaient des symptômes « caractéristiques » ainsi que dans celles de trois personnes apparemment bien portantes qui appartenaient à des familles en contact avec des malades. La concentration du virus dans les selles était élevée et certains patients en ont excrété pendant deux mois ou davantage. Le virus a également été retrouvé dans les eaux usées des deux communautés atteintes par l'épidémie. Une étude sérologique effectuée après l'épidémie sur un nombre plus important de personnes a confirmé le rôle pathogène joué par l'adénovirus du type 3 dans cette épidémie. L'incidence des différents symptômes fut comparable à celle trouvée par Bell et ses collaborateurs, sauf toutefois que les troubles digestifs, tels que nausées, vomissements, gastralgies et diarrhées, furent observés dans plus de la moitié des cas survenus en Suède. L'auteur commente certaines données épidémiologique et les compare à celles recueillies par Bell et ses collaborateurs.

Eine vom Adenovirus Typus 3 verursachte Epidemie unter schwedischen Kindern.

Eine Epidemie von „pharyngo-conjunctivalem" Fieber, welche im Jahre 1955 im Sommer im Landinnern von Schweden ausbrach, ist beschrieben. Eine Wechselbeziehung mit vom Typus 3 des Adenovirus verursachten Infectionen wurde festgestellt. Virus von diesem Typus wurde aus den Stühlen von 23 unter den 25 Kranken mit „typischen" Symtomen isoliert und dazu noch aus den Stühlen von drei anscheinend gesunden Kontaktpersonen in der Familie. Der Titer des fäkalen Virus war hoch und zwei Fälle schieden Virus im Stuhl mindestens durch zwei Monate hindurch aus. Virus wurde in den Abwässern der beiden von der Epidemie betroffenen Gemeinden gefunden. Ein serologisches, bei einer grösseren Zahl von Personen nach der Epidemie durchgeführtes Studium, bestätigte die aetiologische Korrelation des Adenovirus Typus 3 mit der Epidemie. Die Häufigkeit der Symptome war ähnlich wie sie Bell und seine Mitarbeiter gefunden haben mit der bemerkenswerten Ausnahme, dass gastro-intestinale Symptome wie Nausea, Erbrechen, Magenschmerzen und Durchfall in nicht weniger als ungefähr der Hälfte der schwedischen Kinder beobachtet wurden. Gewisse epidemiologische Tatsachen werden erörtert und mit den von Bell und seinen Mitarbeitern gefundenen, verglichen.

Epidemia infantil sueca causada por adenovirus tipo 3.

Descríbese una epidemia de "fiebre faringoconjuntiva" ocurrida en Suecia Central, durante el verano de 1955. Se descubrió una correlación de las infecciones con adenovirus del tipo 3. Por lo tanto, este tipo de virus fué aislado de las heces de 23 entre 25 pacientes con síntomas "típicos" y, además, también de las heces de tres contactos familiares aparentemente sanos. El título de virus fecal fué elevado y algunos casos excretaron el virus en sus heces durante dos meses por lo menos. Se recuperó virus del desagüe cloacal de ambas comunidades implicadas en la epidemia. El estudio serológico realizado después de la epidemia en un grupo mayor de personas, confirmó la correlación etiológica del adenovirus tipo 3 con la enfermedad epidémica. Las frecuencias de los síntomas fueron similares a las halladas por Bell y colaboradores, con la notable excepción de que los síntomas gastrointestinales tales como náusea, vómitos, dolor de estómago y diarrea, se encontraron en nada menos que aproximadamente la mitad de los casos suecos. Discútense algunos datos epidemiológicos y compáranse con los reunidos por Bell y sus colaboradores.

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The Failure of Newborn Premature Infants to Absorb Antibodies from Heterologous Colostrum

by FOLKE NORDBRING

In a previous report (22), based on the determination of antibodies in human colostrum, it has been stressed that antibodies appearing in human colostrum probably are of negligible significance to the newborn infant. The total amount of antibodies reaching the infant, if he is able to absorb them, is in general small. The question, whether antibodies on the whole are absorbed or not by the human newborn infant, is of decisive importance.

There are comparatively few studies concerning this problem in the literature. Reviews of earlier investigations are given by Ratner *et al.* in a series of papers 1927 and 1934 (27, 28, 29) and by McKhann & Kapnick 1938 (17), and the reader is referred to these. In brief, it was shown in the earlier studies that diphtheria antitoxins were not transmitted to the newborn by way of the colostrum or were possibly transmitted in very small amounts, whereas coli agglutinins seemed to be absorbed. It was well established in several investigations, that unaltered or incompletely digested protein could be absorbed by the newborn with subsequent development of an immune response. This occurred in normal infants, although irregularly, and particularly in infants with nutritional disorders.

During the last years some further studies on this topic have been carried out.

Diphtheria antitoxin.—Heller (12) immunized mothers passively at different stages of lactation by injection of horse diphtheria immune serum and compared the titres in the infants' bloods before the experiments and after five days of nursing. A rise in titre was found in only 1 out of 22 sera. The colostrum or milk titres were not stated. Vahlquist & Högstedt (35) gave human serum with a high titre orally within 24 hours after birth to a group of 13 infants and to another group of 14 older infants. Minute amounts of antibodies were found to be absorbed by some infants in the younger group. The amounts usually were less than 0.1 per cent of the total amount administered, in one case the absorption was estimated to ≤ 0.3 per cent.

Agglutinins against enteric pathogens.—Schubert & Grünberg (34) reported extremely high typhoid H agglutinin titres in colostrum of a group of mothers, actively immunized during gestation, but no rise in titre was demonstrated in the sera of the infants at one week of age, the nursing beginning on the second day. They also fed three infants at three hours of age five ml of colostrum with a titre of 1:320,000, but no agglutinins were found in their sera three days later. On the other hand, Petersen & Campbell (26) recently have reported that Salmonella agglutinins in cow's milk are absorbed even by adult humans, and they stated that cow's milk

could be used in prevention of disease. Their figures are, however, not very impressive: five men, who each day consumed one litre of milk with a titre of 1:1,000, showed a rise in titre from 0 to 1:10.

In contrast to earlier findings concerning coli agglutinins, Schneider & Papp (33) were not able to demonstrate absorption of these agglutinins by the infants of a few mothers with fairly high colostrum titres. Sera were obtained from the infants after three to five days of nursing.

Viral antibodies.—Weiss (38) studied the absorption of vaccinia antibodies by way of milk in seven infants. A negligible amount seemed to be absorbed by two of the infants. Sabin (31) stated, that there is no serological evidence of transmission of poliomyelitis antibodies by milk ingestion, judging from large surveys on children, who had been nursed for a long period.

Blood group agglutinins.—Following the demonstration of Rh antibodies in milk, there was some concern about the harmful influence of absorbed antibodies. Cathie (6), however, who fed serum with complete or incomplete Rh antibodies to 12 Rh positive infants, found no absorption of antibodies in any of the infants. No details concerning the age of the infants or the quantity of antibodies administered were given. He concludes, however, that in cases where weaning has appeared to overcome the anemia, the time of weaning has coincided with the time of spontaneous recovery. Broman (5) repeated these experiments, feeding serum with incomplete Rh antibodies to two newborn infants in the course of three days. No absorption was revealed.

Moulinier (21) gave serum-milk mixtures, containing incomplete blood group agglutinins, to three newborn infants. In one, nine days old, absorption of anti-A was demonstrated. Bowman (3) fed sera with complete blood group agglutinins to 16 infants, starting on the first days of life. In one infant, who was 50 hours old, absorption of anti-A was shown, and the amount of antibodies absorbed was calculated to 0.1 per cent of the amount given. Bowman also estimated the quantity absorbed in Moulinier's case to about 0.06 per cent.

Unaltered or incompletely digested protein.—In several investigations it has been confirmed that small amounts of unsplit or incompletely digested protein can enter the blood stream after ingestion, and this appears to occur with such a frequency that it might be considered physiologic. This phenomenon has been studied, using the Prausnitz-Küstner test (37, 8), the precipitin test (15), by determination of specific antibodies against the food protein (15, 16, 2) or by immunochemical analysis (10).

In the last-mentioned work by Gruskay & Cooke, egg albumin was fed to 21 infants (1–13 months old), recovering from diarrhea, and to 19 control infants (5 days to 19 months old) without gastrointestinal disorders. The quantitative precipitin test used allowed exact measurement of the quantity absorbed. Egg albumin was demonstrated in the blood of all infants one or two hours after ingestion, but the absorption by the infants recovering from gastrointestinal disease was significantly higher (about 0.1 per cent of ingested dose) than that of the controls (about 0.02 per cent).

It appears from the studies cited above that the gastro-intestinal wall is permeable to minute quantities of unaltered or incompletely digested protein. Only occasionally do antibodies seem to pass through the wall in such quantities as to give a significant increase in titre in the blood. In these cases human serum has been given.

The antibody level in the blood of the newborn is dependent on the level

in the blood of the mother. Some antibodies apparently are not transferred or transferred in small amounts during the intrauterine life. Premature infants, particularly the small ones, may be born with a somewhat lower concentration of antibodies than full-term infants. Such a tendency has been suggested by Vahlquist, Lagercrantz & Nordbring (36) and Osborn, Dancis & Rosenberg (25). Moreover, a low gamma globulin concentration has been demonstrated in the sera of premature infants of low birth weights (e.g. 20, 32).

Lacking the opportunity of using homologous colostrum with appreciable antibody titre, it was thought to be of interest to find out if antibodies are absorbed from heterologous colostrum by the newborn infant, especially when given very soon after birth. If such were the case, as has been proposed by Petersen & Campbell (26), large amounts of antibody-containing colostrum could be made available, e.g. by vaccinating cows during gestation.

In this paper the results of feeding prematurely born infants antibody-containing heterologous colostrum will be reported.

Material and Methods

Colostrum was secured within the first few hours after parturition from cows and sows, immunized during gestation with a paratyphoid A vaccine, which was prepared in the State Bacteriological Laboratory, Stockholm. The colostrum was handled with extreme cleanliness. The fat was removed by centrifugation under sterile conditions. The skimmed milk was stored in small portions in sterile flasks in the frozen state at $-16°$ to $-20°$C. A standard bacteriological test on pooled samples of the stored colostrum was quite satisfactory. The flask in use was put into the refrigerator and only a small portion, sufficient for one feeding, was warmed up to body temperature but never pasteurized or boiled.

The colostrum used in the feedings was analysed for antibodies. H antigen was prepared in the State Bacteriological Laboratory from the same paratyphoid A strain, used for the vaccine, and the H agglutinin content was determined by the serial dilution test (Widal test). The end point in the readings was the tube, in which a distinct agglutination could be observed by the naked eye. On repeated examinations of several samples of the stored colostrum, both the bovine and porcine colostrum used were found to have an agglutinin titre of 1:10,240.

Nine premature infants were fed such colostrum, six received bovine colostrum, three porcine colostrum. The feedings started at 5 to 25 hours of age and took place in the course of 19 to 45 hours. The colostrum was given slowly by gavage. All infants were in good general condition. A few infants vomited small amounts after some meals, the amounts lost were estimated and the record was adjusted.

Samples of cord blood or maternal blood were obtained at birth. A blood sample was taken from the infants by means of heel puncture 2 to 22 hours after finished feeding. All blood samples were allowed to clot, the serum was sucked off and was stored at $-16°$ to $-20°$C until analysis. Antibody determination was performed on corresponding pairs of sera at the same time. When there is no antibody titre in the

mother's serum, it is quite justifiable to compare this serum with the infant's serum after feeding, because in such a case the infant is born without titre. The Widal test was used with the same antigen as above, beginning at a 1:20 dilution of serum.

Results

The data from the feeding experiments are presented in Table 1. Cases 4, 7 and 9 received porcine colostrum, all others bovine colostrum. In Cases 5 and 9 cord serum was available, in the other ones maternal serum was analysed for comparison.

It is obvious from the table that although the feedings were started soon after birth, no antibodies at all are present in the serum of any infant.

The percentages of the amounts of antibodies given to the infants, which would have had to be absorbed to attain a titre of 1:20, have been calculated.[1] These percentages are recorded in Table 2. It is seen from the table that the amounts of antibodies given to these nine infants are sufficient enough and the method of antibody determination sensitive enough to

TABLE 1

Record of experiments on transmission of paratyphoid H agglutinins by way of heterologous colostrum to newborn prematures.

Case no.	Birth weight in g	Amount col. given in ml	Number of feedings	Age in hours when feeding		Age in hours when blood sample was taken	Titre H aggl.	
				started	finished		before	after
1	1440	36	9	5	27	30	0	0
2	1020	54	11	5	50	72	0	0
3	2370	66	11	6	30	33	0	0
4	2170	60	8	6	25	30	0	0
5	1590	66	9	12	36	43	0	0
6	1050	32	9	12	36	43	0	0
7	1810	44	8	12	31	38	0	0
8	1890	80	11	24	64	76	0	0
9	2130	67	8	25	48	50	0	0

[1] The following formula was used:

$$\frac{\frac{p}{100} \times \text{volume colostrum in ml} \times \frac{1}{\text{colostrum titre}}}{\text{volume of distribution in ml}} = \frac{1}{\text{serum titre}},$$

where p = per cent antibodies absorbed. The volume of distribution for homologous antibodies is close to the plasma volume (35), and the approximation has been made in the formula, that the volume of distribution is equal to the plasma volume. The plasma volume was estimated to be 4.1 per cent of the body weight (19).

TABLE 2

The required absorption of antibodies (as per cent of the amount given) to attain an agglutinin titre of 1:20 is recorded in the left column. The amounts of colostrum with a titre of 1:10,240, required to attain a titre of 1:20 in the infant's blood under the assumption of 0.1 or 0.02 per cent absorption, are recorded in remaining columns.

Case no.	Per cent of antibodies to be absorbed to attain a titre of 1:20	Required amounts of col. in ml to attain a titre of 1:20, assuming an absorption of	
		0.1 %	0.02 %
1	0.32	115	576
2	0.15	82	408
3	0.29	190	949
4	0.29	174	869
5	0.19	127	637
6	0.26	84	421
7	0.33	145	725
8	0.19	151	757
9	0.25	171	853

conclude, that if absorption has taken place at all, the quantity of antibody absorbed has been less than 0.15–0.33 per cent of the quantity given. Because of the small number of infants, it can of course not be stated, that this is generally true. However, the 95 per cent lower confidence limit is 72 per cent.

In Table 2 also are recorded, for comparison, the amounts of the colostrum used in this investigation, which would have had to be given to attain a titre of 1:20 on the assumption of 0.1 or 0.02 per cent absorption. As has been mentioned previously, the quantity of antibodies occasionally found to be absorbed in some investigations has been estimated to about 0.1 per cent of given dose, and Gruskay & Cooke, using a very exact method, found that whole protein normally is absorbed to an extent of 0.02 per cent.

As is seen from the table, large quantities of the colostrum would be necessary.

Discussion

It is evident from this study that the absorption of the antibodies in question by the newborn premature infant is so small, if it occurs at all, that heterologous colostrum hardly could be used for the purpose of supplying the newborn with antibodies of this type. In these experiments an absorption percentage of 0.15–0.33 would give an H agglutinin titre not

higher than 1:20. It is possible that some minute absorption occurred, although this could not be revealed in the experiments. Much larger amounts of the colostrum available would have to be given in order to prove this assumption (Table 2) or much higher titre in the colostrum would be required (with the amounts given to the infants the range of colostrum titres required to attain a titre of 1:20 in the case of 0.02 per cent absorption would be from 1:81,920 to 1:327,680). Even if these stipulations had been met, only a low titre would be found in the infant's blood.

In this investigation only paratyphoid H agglutinins have been studied and the poor absorption of these antibodies might not necessarily be true for other antibodies. In view of the results of earlier work, mentioned previously in this paper, it however appears to be true for several other antibodies studied.

Many factors are involved in development of resistance to infectious disease and the appearance of humoral antibodies is only partly responsible for the immunity state. It is thus difficult to define a certain antibody level, required for protection, but it seems unlikely that appreciable amounts of antibodies could be gained via heterologous colostrum.

It is possible that the antibodies given have been destroyed, due to gastric acidity, or digested. Although there is some controversy concerning the development of the digestive apparatus in the premature infant, recent studies indicate that proteins are digested to a great extent (9, 1). Trypsin appears in the duodenal juice in an amount equal to that of the full-term infant (18). The possibility of a breakdown of the antibodies thus exists.

On the other hand, there is evidence from in vitro studies on enzymatic digestion that the antibody molecule may be split into half the size and yet retain the antibody property, however, at a low pH the antibody is destroyed (4, 7, 23, 30). Moulinier, in his before-mentioned study (21), obtained gastric juice from newborn full-term and premature infants and Rh sera were digested for one hour at + 37°C. There was no reduction in titre, when pH was above 4. It has also been reported (34) that typhoid agglutinins were found in the stools of infants, fed colostrum with a high titre of agglutinins. Thus it seems likely that antibodies might to a certain extent escape the proteolytic digestion and might be absorbed, although the last mentioned observation indicates that they might pass through the gastrointestinal tract, unaltered or partly digested, without being absorbed.

As has been demonstrated in this investigation, only very small amounts if any of antibody protein in *heterologous* colostrum are absorbed. The objection might be raised that antibodies occurring in *homologous* colostrum might reach the blood of the infant more readily, because of some unknown

mechanism of easier transmission through the mucous membrane or because of higher protection against the proteolytic digestion. However, in earlier investigations it has repeatedly been shown, that undigested or partly digested foreign proteins may be absorbed, even though the amounts are small (e.g. 15, 8).

Laskowski & Laskowski (14) demonstrated in 1951 the occurrence of a potent trypsin inhibitor in human colostrum with a maximal appearance between the first and third days after delivery, and they suggested that the presence of this inhibitor could explain how "immune globulins" escape digestion. However, the inhibitor was also demonstrated in cow's colostrum and in a higher concentration than in human colostrum. Besides, such an inhibitor has been found in high concentration also in swine colostrum (13, 11).

It is of interest in this discussion that antibodies can easily be absorbed by the newborn piglet from bovine colostrum (24). The development of the digestive apparatus in the newborn piglet is incompletely studied, but it has been observed that stool dilutions digest the gelatinous coating of photographic film (24). These animals, for which the absorption of antibodies by way of colostrum is vital, obviously can make use of heterologous colostrum as well.

The findings in earlier investigations cited in this paper and the results of the present study, as far as comparisons between homologous and heterologous colostrum can be made, give further emphasis to the statement in the introduction to this paper that antibodies in human colostrum are of negligible importance to the newborn infant. Because of the minute absorption, which possibly occurs, the antibody titre in the colostrum must either be extremely high or the infant must consume large quantities of the antibody-containing colostrum to acquire an appreciable titre. Neither of these alternatives is likely to occur, because very high titres appear only occasionally in human colostrum, and the antibodies decrease in titre or disappear at the time, when milk production increases.

Summary

Nine premature infants have been fed heterologous colostrum, containing paratyphoid H agglutinins. The feedings started soon after birth. None of these infants showed an agglutinin titre in their sera after feeding. It was calculated that the absorption, if any, must have been less than 0.15–0.33 per cent of the amounts of antibodies given.

The significance of these findings is discussed together with information, available in the literature. It is concluded that the demonstrated poor absorption ability gives further emphasis to the opinion, that antibodies in colostrum play a negligible rôle for the newborn.

Impuissance des nouveau-nés prématurés à absorber les anticorps du colostrum hétérologue.

Neuf prématurés ont reçu du colostrum hétérologue contenant des agglutinines paratyphoides H. Les têtées commencèrent peu de temps après la naissance. Pour aucun des nourrissons, la têtée ne fut suivie d'un titre d'agglutinines dans le sérum. L'auteur estime que l'absorption, si elle a lieu, est de moins de 0,15 à 0,33 % de la quantité d'anticorps administrée. Il discute l'importance de ses constatations et de celles d'autres auteurs et conclut que l'impuissance à absorber ainsi démontrée vient à l'appui de l'opinion selon laquelle les anticorps du colostrum jouent un rôle négligeable pour le nouveau-né.

Ausbleibende Antikörperabsorption aus heterologem Kolostrum bei frühgeborenen Kindern.

Neun frühgeborene Kinder wurden mit heterologem, Paratyphus H Agglutinine enthaltenden Kolostrum, gefüttert. Die Fütterung begann bald nach ihrer Geburt. Keines der Kinder wies einen Agglutinintiter im Serum nach der Fütterung auf. Es wurde berechnet, dass, wenn Absorption überhaupt stattfand, sie geringer war als 0,15–0,33 pro Hundert der verabreichten Antikörper. Die Bedeutung dieser Befunde wird im Zusammenhang mit Berichten aus dem Schrifttum besprochen. Der Schluss wird gezogen, dass die nachgewiesene geringfügige Absorption die Annahme, dass im Kolostrum vorhandene Antikörper eine unwesentliche Rolle beim Neugeborenen spielen, vollauf bekräftigt.

Incapacidad de los prematuros neonatos para la absorción de anticuerpos provenientes de calostro heterólogo.

Administróse por vía alimentaria a nueve prematuros calostro heterólogo conteniendo aglutininas H paratifoidicas. Las ingestiones se iniciaron poco después del nacimiento. Ninguno de estos niños presentó tras ingestión un título sérico de aglutinación. Según ha podido calcularse, la absorción, si tuvo lugar, debe haber sido de un orden inferior a 0,15–0,33 por ciento de las cantidades de anticuerpos administradas. La significación de estos hallazgos se discute al propio tiempo que la información bibliográfica. Sácase la conclusión de que la inferioridad de la facultad de absorción comprobada, acentúa con mayor énfasis todavía el criterio de que los anticuerpos en el calostro, para el recién nacido juegan un papel despreciable.

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On the Variability of the Clinical Course of Congenital Toxoplasmosis with Special Reference to the Occurrence of Mild Cases

by GRETA HEDENSTRÖM

Toxoplasmosis acquired after birth may be severe or mild. Some cases present more or less extensive involvement of the brain, eyes, heart, lungs, the skin and occasionally of other organs. On the other hand the occurrence of milder cases with local or generalized lymphadenopathy with or without fever seems to be not infrequent in Scandinavia. Finally, infections without any clinical signs at all are more frequently encountered than other types of acquired toxoplasmosis.

In case of congenital toxoplasmosis the situation seems quite different. Several cases have been reported, in which the destructive action of the Toxoplasma organisms apparently is restricted to one of the patient's eyes, causing chorioretinopathy, occasionally accompanied by a squint. In this connection the probability of the occurrence of mild cases of congenital toxoplasmosis has been stressed by several authors. Nevertheless the general concept of congenital toxoplasmosis (10, 13, 18) is dominated by the classical severe variety of the disease.

It has been suggested that the embryo might be more susceptible to toxoplasmic infection than the human organism after birth. Such is known to be the case in some viral infections. This is probably true in some degree. The classical combination of destructive meningo-encephalitis, leading to cerebral calcifications and hydrocephalus, and chorioretinitis or other severe damage to the eye, is a relatively frequent variety of congenital toxoplasmosis. It is mostly in such cases however that the diagnosis has been suspected, serological testimony sought, and a diagnosis of congenital toxoplasmosis has been established. The milder cases may be found more frequently, if they were more often looked for.

In less than one year three infants from the county of Jämtland in the North of Sweden and examined in the Pediatric Department of the County Hospital in Östersund were found to be suffering from congenital toxo-

plasmosis. While two of them presented the classical severe type of the disease, one girl had as her sole complaint a benign convulsive disorder and was otherwise found to be healthy and well developed.

Case Report

CASE 1.—E. K. M., a girl born at term June 8, 1954, seemed completely healthy when examined a few days after birth, when she weighed 4100 g.

She was a first-born child. Her mother had her tonsils removed in May in 1953 because of persistent infections. Three months later she aborted but after another three months she was again pregnant and gave birth to our patient in June 1954. The child was wholly breastfed during the first five months of life.

Between the age of 2½ and 5 months she had six attacks of generalized convulsions, each attack leaving her unconscious for about one minute.

Since the age of five months she has never had any convulsions, but she has suffered from minor attacks of seizures—petit mal—now and then. Whenever she becomes acutely infected or exposed to unaccostumed surroundings she may have several attacks a day. When nothing extraordinary disturbs her she has been completely free from attacks for many weeks without any anticonvulsive therapy. Her physical and mental development has been satisfactory, even rapid. She could walk at the age of 11 months and speak a few words at 15 months. She is active and happy, but not restless.

She has never shown any signs of spasticity or rigidity. No cerebral calcifications are seen in the X-ray films. Her eyes are completely free from pathological signs. Her ECG show nothing abnormal, nor the one EEG that has so far been performed.

A lumbar punction at the age of five months gave a fluid of normal composition. All her blood values have been within normal limits.

The serological data are listed in the table. The child's father is serologically negative.

Case 1. Serological data.

Date 1954	Mother		Child	
	Dye test	CFT	Dye test	CFT
11/11	1/1,250	1/30		
26/11			1/250	(impossible to interpret)
1955				
11/1	1/250	1/7,5	1/250	1/7,5
15/3	1/250	neg.	1/1,250	neg.
30/6	1/250	neg.	1/250	neg.
21/9	1/50	neg.	1/250	neg.
8/11	1/50	neg.	1/50	neg.
1956				
21/4	1/10	neg.		

Discussion.—The mother's serological data indicate that she probably suffered from toxoplasmosis in an active stage during her last pregnancy. It is difficult to say, however, if her miscarriage three months previously was provoked by this infection, although it seems probable.

The child presented the same dye test titer of 1/250 at 15 months as at 5 months. The serological findings in her blood consequently cannot be due to a passive placental transfer of antibodies from her mother. The child must have been actually infected with Toxoplasma organisms. The possibility that she may have acquired her toxoplasmosis after birth, and probably from her mother, cannot be excluded. A congenital infection seems however more likely.

During the same year as the above-mentioned infant three other children from the county of Jämtland were found to suffer from cerebral and ophthalmic destruction, probably due to congenital toxoplasmosis. In Case 2 the diagnosis was made in the University Hospital in Uppsala and I owe my knowledge of this patient to the courtesy of Professor B. Vahlquist.

CASE 2.—K. J., a boy born 3 weeks before term, has suffered with convulsions since the age of 6 months. The convulsions engage mostly the left side of the body, but can be fairly well controlled by the use of phenobarbitone (Phenemal) in small quantities. He has also a squint. He could walk at the age of 14 months and could speak a few words when 2 years old. He is extremely troublesome to manage and gets angry very easily. He seems slightly mentally retarded.

His mother was not ill in any way before or during her pregnancy. She is a trained nurse and worked in an infectious hospital when pregnant.

A pea-sized calcification was seen in the X-ray films of the boy's skull. It was localized to the middle of the occipital area.

There is chorioretinopathy in both eyes. The left macula is involved and the boy has a squint.

In the EEG a spike focus can be seen in the right temporal area.

The ECG is quite normal and the blood values within normal limits.

Serological data (the samples were taken when the boy was 3 years old):

Mother		Child	
Dye test	CFT	Dye test	CFT
1/50	1/7.5	1/50	1/120

Comment.—The combination of chorioretinopathy and cerebral calcification make a diagnosis of congenital toxoplasmosis probable, while the presence of antibodies in the blood of both mother and child support the diagnosis.

CASE 3.—S. A. D., a girl born at term, was brought to examination because of suspected mental retardation. At the age of 1 year 3 months she was unable to sit erect

without support and had made no efforts to speak. Three months later she could sit by herself and could say "Ma-ma".

Her mother, who had given birth to a healthy child a few years earlier, enjoyed excellent health during her last pregnancy.

The child showed no signs of spasticity or rigidity. She had no convulsions.

An X-ray film of her hips revealed nothing abnormal. She had no cerebral calcifications.

In her left eye she had a chorioretinopathy in the macular region.

Serological data (the child's birth date: 17/10 1953):

Date	Child		Mother	
1955	Dye test	CFT	Dye test	CFT
$^{11}/_{1}$	1/250	1/30		
$^{29}/_{1}$			1/250	1/30
$^{6}/_{10}$	1/50	1/15	1/50	negative

Comment.—Both mother and child have been infected with toxoplasmosis. The antibody titers in the child's blood are too persistent to have been passively and placentally transmitted from her mother during the pregnancy. The toxoplasmic infection probably is responsible for her chorioretinopathy and her mental retardation.

Conclusions

If the evidence of congenital infection is accepted in the first case, then she represents a course of congenital toxoplasmosis, in which the destructive action of the Toxoplasma organisms was restricted to a limited area of the brain. The eyes were not affected.

It cannot as yet be definitely stated if such a restricted involvement of brain tissue is an ordinary or an exceptional occurrence in congenital toxoplasmosis.

From the two reported cases and from reports in the literature it is possible to conclude however that congenital toxoplasmosis varies in severity from case to case. Relatively benign cases are probably not rare, if looked for.

All serological and parasitological data have been kindly provided by Dr. Gunnel Huldt at Statens Bakteriologiska Laboratorium, Stockholm.

Summary

Report of a case of serologically verified congenital toxoplasmosis. This child had six attacks of convulsions between the age of 2½ and 5 months. Later she has suffered only from petit mal of various frequency. More than a month may pass without any seizure. Mental and somatic development is normal. The brain shows no calcifications, the EEC is normal and the eyes are intact.

Two other children with the probable diagnosis of congenital toxoplasmosis and with different constitutional involvement are reported.

There is good evidence available that congenital toxoplasmosis occurs both in mild and in severe forms.

Inconstance de l'évolution clinique de la toxoplasmose congénitale avec mention particulière de l'incidence de cas bénins.

Rapport d'un cas de toxoplasmose congénitale vérifiée par examen sérologique. L'enfant fit six crises de convulsions entre deux mois et demi et cinq mois. Ensuite, elle eut des crises de petit mal à différents intervalles. Parfois, plus d'un mois séparait deux crises. Son développement mental et somatique était normal. Il n'y a pas de calcification cérébrale; l'EEG était normal et les yeux intacts. L'auteur rapporte deux autres enfants avec un diagnostic probable de toxoplasmose congénitale bénigne, mais avec des manifestations constitutionnelles différentes. Il y a des preuves suffisantes que la toxoplasmose congénitale se manifeste à la fois sous les formes bénigne et sévère.

Über die Verschiedenheit im klinischen Verlauf der angeborenen Toxoplasmose mit besonderem Hinweis auf das Vorkommen leichter Fälle.

Bericht über einen Fall serologisch nachgewiesener angeborener Toxoplasmose. Das Kind hatte 6 Anfälle von Krämpfen im Alter von 2½ bis zu 5 Monaten. Später litt sie nur an petit-mal-Anfällen von verschiedener Häufigkeit. Mehr als ein Monat kann ohne Anfälle vorübergehen. Die geistige und körperliche Entwicklung ist normal. Das Hirn weist keine Verkalkungsherde auf, das EEG und die Augen sind in Ordnung. Zwei weitere Kinder mit der wahrscheinlichen Diagnose einer benignen angeborenen Toxoplasmose mit verschiedenen konstitutionellen Symptomen werden angeführt. Es besteht Beweis dafür, dass die angeborene Toxoplasmose sowohl in einer milden als auch schweren Form auftreten kann.

Variabilidad del curso clínico de la toxoplasmosis con referencia especial a la ocurrencia de casos leves.

Relátase el caso de una toxoplasmosis congénita comprobada serológicamente. La niña sufrió seis ataques convulsivos entre las edades de 2½ y 5 meses. Más tarde solamente sufrió pequeño mal con frecuencia variable. Pudo transcurrir más de un mes sin producirse ataque repentino. Normales desarrollos mental y somático. Cerebro sin calcificaciones, EEG normal, ojos intactos. Relátanse los casos leves de dos otros niños con diagnosis probable de toxoplasmosis congénita y distintas implicaciones constitucionales. Existe buena evidencia de que la toxoplasmosis congénita se presenta en ambas formas leve y grave.

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The Serum Vitamin B_{12} Levels at Various Ages

by ANDREAS KILLANDER

Compared to the numerous reports on the serum vitamin B_{12} concentrations in various diseases, little attention has been paid to the serum levels of the vitamin in haematologically healthy persons at various ages. A study of the literature reveals four investigations covering a wide range of age.

(1) Mollin & Ross (1952) using *Euglena gracilis* as test organism, assayed the serum vitamin B_{12} levels of three groups: 15–40, 51–70 and 71–93 years of age. The last group showed significantly lower values than the other two. (2) Boger, Wright, Strickland, Gylfe & Ciminera (1955) used a modified *Lactobacillus leichmannii* method for the investigation of three groups of mental hospital patients and one group of male blood donors. In three of the groups there was a slight but statistically significant trend to lower serum vitamin B_{12} concentrations with increasing age. No difference was noted between men and women. (3) Chow, Wood, Horonick & Okuda (1956) using *Lactobacillus leichmannii* as test organism studied the serum vitamin B_{12} levels of three groups of subjects. From the results they concluded that in all groups there was less vitamin B_{12} in the serum with increasing age. (4) Kristensen (1956), employing the same organism, did not find any difference between 55 subjects, 20–40 years of age and 29 cases 67–88 years old. Several other authors have published data on the serum concentration of this substance in normal subjects and patients with pernicious anaemia However, the range of the control subjects' ages was either too narrow or the ages were not stated at all.

Low values of serum vitamin B_{12} during pregnancy were noted by Heinrich (1954). The results were later confirmed by Boger, Wright, Beck & Bayne (1956) and by Okuda, Helliger & Chow (1956). As to the serum vitamin B_{12} concentrations in childhood only a few investigations have been published. In collaboration with Vahlquist I have earlier (Killander & Vahlquist 1954) demonstrated a significantly higher concentration of serum vitamin B_{12} in the umbilical cord blood than in the mother's blood. No differences were found between premature and term infants, 1–83 days old. Recently, Okuda and coworkers (1956) and Boger, Wright & Bayne (1957) have shown higher values of serum vitamin B_{12} in the baby than in the mother at delivery. The serum vitamin B_{12} levels of infants and children were studied together with Söderhjelm (Killander & Söderhjelm 1956). We did not find any differences between haematologically normal children and those suffering from anaemia due to nutritional disturbances or to chronic disease. The mean serum vitamin B_{12} concentration of the children was higher than that of adults.

The level of the vitamin B_{12} in serum is known to be low in diseases due to deficiency of the vitamin. On the other hand high values have been found in chronic myelocytic leukemia and occasionally in acute leukemia. Moderately elevated serum vitamin B_{12} levels are met with in some cases of acute leukemia, polycythaemia vera, liver cirrhosis and diabetes mellitus. However, to be able to state whether the serum vitamin B_{12} is low, normal or elevated it is neccessary to compare with appropriate controls.

This paper presents studies on the serum vitamin B_{12} levels of both sexes at various ages from birth to 82 years. The investigations on the serum content of vitamin B_{12} in childhood, referred to above, have been extended and the results subjected to statistical treatment in order to evaluate a possible association between the vitamin B_{12} content of the serum and age, sex and pregnancy.

Comparisons have thus been made between (*a*) baby and mother at delivery, (*b*) mother at delivery and other women of the same age, (*c*) males and females, (*d*) children and adults, and (*e*) young and old adults.

Material

Baby and mother at delivery.—Thirty-two pairs of samples were simultaneously taken from the umbilical cord and an antecubital vein of the mother. Only healthy mothers of full term infants were included. All cases were delivered in the Department of Obstetrics at the University Hospital, Uppsala. Eleven pairs have been published before. The remaining 21 were collected and assayed in collaboration with Dr. T. Mellbin. The investigation was performed from November 1953 to May 1954.

Infants and children.— Forty-five subjects from 1 month to 14 years of age were hospitalized for various reasons in the Department of Pediatrics at the University Hospital, Uppsala and the Central Hospital in Skellefteå. Children with haematological, hepatic, renal, gastro-intestinal, nutritional and endocrine disorders were excluded.

Adults.—There were 165 cases, 89 males and 76 females from 15 to 82 years of age. Forty-five of these were healthy blood donors, 17 to 47 years old. The remaining subjects were hospitalized for various reasons, but care was taken to exclude those who suffered from haematological, hepatic, renal, gastro-intestinal, nutritional or endocrine disorders. Patients with signs of decompensated cardiac failure and of subacute combined degeneration of the cord were also excluded. Haematologically normal values were defined according to Vahlquist (1948). Three standard deviations were used as limits. Most of the patients were treated at the University Hospital in Uppsala (Departments of Internal Medicine, Ophthalmology and Oto-Rhino-Laryngology). The remainder included subjects from the Department of Neurology of the Serafimer Hospital in Stockholm, the Departments of Internal Medicine and Ophthalmology at the Central Hospital in Falun and the Department of Medicine of the Central Hospital in Östersund.

Methods

Venous blood was drawn into sterile glass tubes and allowed to clot at room temperature. The samples were then sent to the Department of Medical Chemistry in Uppsala

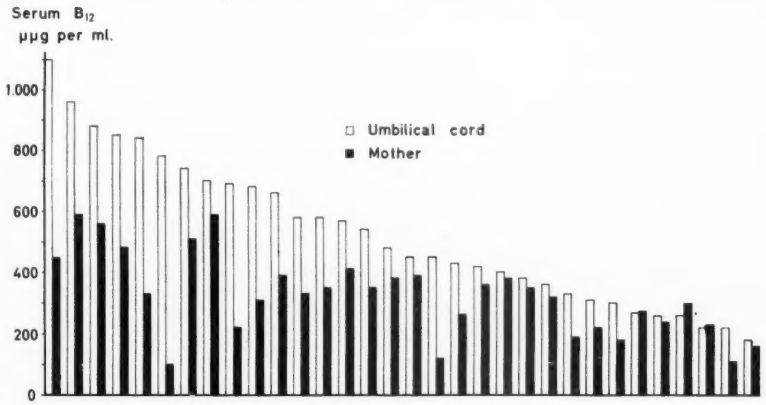

Fig. 1. The serum vitamin B_{12} levels of 32 pairs of infant and mother at delivery arranged according to the serum concentrations of the vitamin in the infants.

as soon as possible. The serum was separated within 36 hours after the sampling and kept frozen until used. The vitamin B_{12} content was assayed microbiologically with *Euglena gracilis* var. *bacillaris* using the method of Ross with some modifications (Killander 1957). Thus the growth of the algae is estimated after 10 days incubation with aid of photometric determination of the pigments after extraction with ethanol. The vitamin B_{12} activities of the sera in two or three dilutions are calculated from a standard curve which represents the growth response of the test organism to solutions with known concentrations of the vitamin. The results are expressed as the vitamin B_{12} concentration of the sample.

Results

The individual observations are represented in Figs. 1 and 2 with age and sex indicated. To facilitate comparison, the mean values, the standard deviations and the significance of the found differences are also tabulated (Tables 1 and 2).

Fig. 1 shows the serum vitamin B_{12} levels of baby and mother at delivery. In 29 of the 32 pairs of samples, the serum concentration of the vitamin was higher in the umbilical cord. The reverse was found in the remaining three but the differences do not exceed the error of the method. The serum vitamin B_{12} levels of the mother ranged from 13 to 115 per cent of those of the babies with a mean of 69 per cent.

The mothers, 19 to 38 years old, also showed a significantly lower mean value of the serum vitamin B_{12} than non-pregnant women in the age group of 20 to 39 years (Table 2).

In Fig. 2 the means of the serum vitamin B_{12} values have been given

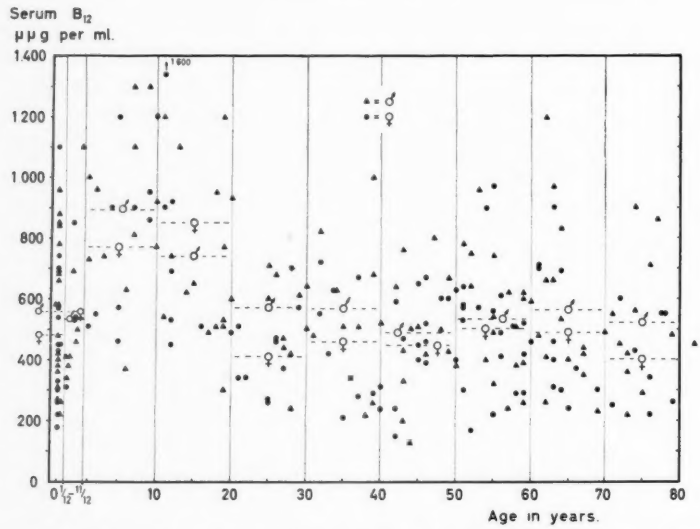

Fig. 2. The serum vitamin B_{12} levels of 242 males and females at various ages. The means of the age groups are indicated by broken lines.

separately for men and women, divided in decades of age. As shown in the diagram the range is wide in all ages. Over 20 years of age women have a slightly lower average serum concentration of the vitamin than men of the same age. The difference is significant (Table 2).

As to variation of the serum vitamin B_{12} with age it is evident that the highest values are met with from 1 to 19 years in both sexes. Significant differences were found between males 1–19 and those 20–39 years old (Table 2). The same degree of significance was also found for the difference between males and females less than one year old and subjects of both sexes 1 to 9 years of age (Table 2).

On the other hand no evidence was found of lower values of the serum vitamin B_{12} concentration in aged subjects. Differences between men 20–39 years of age and those more than 70, as well as between women 50–59 years old, which in this material showed the highest values, and those more than 70, were not significant.

Discussion

It is evident that newborn infants as a rule have a higher content of vitamin B_{12} in the serum than their mothers. The biological significance of this finding is not known, but in this connection it may be recalled that the

TABLE 1

Serum B_{12} concentrations, μμg per ml, of males and females of different age groups.

Age (years)	Males			Females			Comment
	No. of cases	Mean	S.D.	No. of cases	Mean	S.D.	
Newborns (cord blood)	32	527	242				♂+♀
05/12–11/12	12	543	232				♂+♀
1–9	10	894	296	9	767	253	
10–19	16	738	271	8	850	396	
20–29	10	570	189	10	408	106	
30–39	11	568	225	9	457	190	
40–49	14	489	192	15	449	161	
50–59	18	534	197	21	504	199	
60–69	15	562	268	12	487	211	
70–79	12	518	202	8	400	153	
80–	1	440					

Note.—The mean value and the standard deviation for 156 men and women 20 to 82 years of age was 501, and 200 μμg per ml respectively.

TABLE 2

Comparison between the serum vitamin B_{12} levels of different groups.

Groups	Age (years)	No. of cases	Mean	S.D.	Significance of difference
Newborns	(Cord blood)	32	527	242	$p < 0.001$
Mothers	19–38	32	326	133	
♀	20–39	19	431	149	$0.01 < p < 0.05$
Mothers	19–38	32	326	133	
♂	20–82	81	538	210	$0.01 < p < 0.05$
♀	20–79	75	461	177	
♂	1–19	26	798	286	$0.001 < p < 0.01$
♂	20–39	21	569	204	
♂+♀	1–9	19	834	277	$0.001 < p < 0.01$
♂+♀	0.5/12–11/12	12	543	232	

same phenomenon has been proved for other substances, e.g. the serum iron and the amino acids.

The reason of the lower values of the serum vitamin B_{12} in late pregnancy also remains obscure. It is not known at present whether and if so to what

extent the lower values may be explained by simple haemodilution. Obviously a foetal demand exceeding the ability of the mother to resorb the vitamin from the food would lead to a relative deficiency. However neither the size of the foetal demand nor the capacity of a healthy woman on satisfactory diet to resorb and utilize vitamin B_{12} during pregnancy are known. Badenoch, Callender, Evans, Turnbull & Witts (1955) in an investigation of women suffering from megaloblastic anaemia of pregnancy, with the aid of the radioactive vitamin B_{12} test demonstrated a normal resorption of the vitamin. Ross & Mollin (1957) found the total amount of vitamin B_{12} stored in the liver of newborn infants to be small in comparison with the stores of the adult liver. They considered it improbable that the requirements of the foetus would exhaust the mother's supply of the vitamin unless extraordinarily large amounts of vitamin B_{12} are needed for the growth of the foetus.

In this material women over 20 years of age showed a lower mean concentration of the serum vitamin B_{12} than men of the same age. The difference is significant but slight in comparison with the wide range, found for both sexes in all ages. Boger and coworkers did not find any sex difference with regard to the serum vitamin B_{12} concentrations. As to variation of the serum vitamin B_{12} values with age, significantly higher values were found in both sexes in the age group of 1 to 19 years. There was no evidence of lower values in old subjects, which is in contrast to the findings of three of the four workers, cited in the beginning of this paper. The reasons of these discrepancies are not clear. Obviously, the material of this investigation as well as those presented by other workers, represent selected groups. A strict comparison between the results is therefore difficult.

A study of the papers published on this problem reveals some conflicting results. As mentioned before, Kristensen found no difference between young and old subjects. Mollin & Ross found significantly lower values only in the subjects 71 to 90 but not in individuals 51 to 70 as compared with subjects 15 to 40 years of age. Boger and coworkers[1] studied four groups of subjects, of which three were composed of patients of mental institutions, and one of healthy male blood donors. Lower levels of serum vitamin B_{12} with increasing age were found in three of the groups but the slopes of the regression lines were different. In the remaining group, consisting of 108 institutionalized males about 15 to 85 years old, no differences were found. Chow *et al.* found lower serum vitamin B_{12} levels with increasing age in three groups, of which two consisted of institutionalized subjects. The third

[1] The results are given in diagrams to which the reader is referred.

TABLE 3

Serum vitamin B_{12} concentrations, $\mu\mu g$ per ml.

Chow *et al.* (1956)				Kristensen (1956)				Mollin & Ross (1952)			
Age (years)	No. of cases	Mean	S.D.	Age (years)	No. of cases	Mean	S.D.	Age (years)	No. of cases	Mean	S.D.
10–19	10	284	101					15			
20–29	19	249	72	20							
30–39	33	235	111		55	365 (150–685)	—		65	358	130
40–49	31	240	111	40				40			
50–59	10	210	65					51			
									27	322	150
60–69	6	214	100					70			
								71			
				67							
70–79	5	90	29		29	395 (190–770)	—		31	259	176
80–89				88							
90–								93			

was composed of 114 "randomly" selected individuals from 10 to more than 70 years of age. As shown in Table 3 the decrease of the serum vitamin B_{12} with age was irregular, with a sudden drop in the five subjects over 70 years old. It must also be remembered that these workers used a technique of assay which differed from the others discussed in this connection in that they precipitated the serum proteins prior to the analysis. Unfortunately cyanide was not added before the precipitation and as demonstrated earlier (Killander, 1957), such a procedure reduces the vitamin B_{12} activity of the serum with 47–76 per cent of the values found without precipitation. The serum vitamin B_{12} values, in all ages significantly lower than those reported by Mollin & Ross, Boger and coworkers, Kristensen and this paper, might possibly be explained by the loss of vitamin B_{12} activity during the preparation of the samples.

It is not apparent to what extent the discrepancies between the serum vitamin B_{12} values of "normal subjects" at various ages might be explained by dissimilarities in the composition of the groups or by the use of different techniques of assay. In view of the wide normal range found by all investigators, the significant differences between the mean serum vitamin B_{12} levels and the great error involved in the microbiological assay of serum vitamin B_{12} it is probable, however, that both factors play an important role.

The discrepancies also illustrate the need for each investigator in this field to determine the normal range under his own conditions of assay. At present the importance of knowing the serum vitamin B_{12} levels of both sexes at various ages lies in the establishment of the normal limits with the technique of assay used. The biological significance of the lower levels of vitamin B_{12} in the aged, reported by other workers, and the high serum vitamin B_{12} concentration of children and youths demonstrated in this paper, remains obscure.

Summary

An investigation of the relation between serum vitamin B_{12} levels and age and sex of 242 haematologically normal subjects, 0 to 82 years of age was performed.

The serum vitamin B_{12} content was determined microbiologically using *Euglena gracilis* var. *bacillaris*.

The range of the serum vitamin B_{12} values was found to be wide in both sexes at all ages. The serum vitamin B_{12} concentrations of newborn infants were significantly higher than those of the mothers ($p < 0.001$). The latter also had less vitamin B_{12} in the serum than non-pregnant women of the same age ($0.01 < p < 0.05$).

The highest values of serum vitamin B_{12} were encountered in the age group 1 to 19 years.

Men 20–82 years of age showed a higher mean serum vitamin B_{12} concentration than women of the same age. The difference was significant ($0.01 < p < 0.05$). In contrast to the findings reported by most other workers, there was no evidence in this investigation of a decrease of the vitamin B_{12} concentrations in serum with increasing age.

The results presented here and those reported by other investigations were discussed.

The biological significance of the differences found between the serum vitamin B_{12} levels of different groups of haematologically normal subjects is not apparent.

Taux du sérum en vitamine B_{12} à des âges différents.

L'auteur a étudié le rapport entre le taux du sérum en vitamine B_{12}, l'âge et le sexe de 242 sujets hématologiquement normaux entre 0 et 82 ans. *Euglena gracilis* var. *bacillaris* servit à la détermination microbiologique de la teneur du sérum en vitamine B_{12}. Le taux varie considérablement pour les deux sexes à tous les âges. Il est significatif que les concentrations des nouveau-nés sont plus fortes que celles de leur mères. Ces dernières ont aussi moins de vitamine B_{12} dans leur sérum que les femmes du même âge qui ne sont pas enceintes. Les concentrations les plus fortes se rencontrent entre 1 et 19 ans. La concentration moyenne des hommes de 20 à 82 ans est plus forte que celle des femmes du même âge. La différence est significative. Contrairement aux résultats de la plupart des autres chercheurs, cette investigation n'a pas démontré que les concentrations diminuent avec l'âge. L'auteur discute ses résultats et ceux obtenus par d'autres chercheurs. Il n'est pas évident que les différences de taux du sérum en vitamine B_{12} chez différents groupes de sujets hématologiquement normaux aient une importance biologique.

Die Vitamin-B_{12}-Spiegel im Serum in verschiedenen Lebensaltern.

Eine Untersuchung über das Verhältnis des Vitamin-B_{12}-Spiegels im Serum zum Alter und Geschlecht von 242 hämatologisch normalen von 0–82 Jahre alten Personen wurde durchgeführt. Der Vitamin-B_{12}-Gehalt im Serum wurde mikrobiologisch mit Hilfe der *Euglena gracilis* var. *bacillaris* bestimmt. Es wurde gefunden, dass der Bereich der Vitamin-B_{12}-Werte im Serum bei beiden Geschlechtern in allen Altern sehr gross ist. Die Konzentration von Vitamin B_{12} im Serum von neugeborenen Kindern war bedeutend grösser als die der Mütter. Die letzteren hatten auch weniger Vitamin B_{12} im Serum als nicht-schwangere Frauen im selben Alter. Die höchsten Werte von Vitamin B_{12} im Serum wurden in der Altersgruppe von 1–19 Jahren angetroffen. Männer zwischen 20 und 82 Jahren wiesen eine höhere durchschnittliche Vitamin-B_{12}-Konzentration im Serum auf als Frauen desselben Alters. Der Unterschied war bedeutsam. Im Gegensatz zu den von den meisten Arbeitern mitgeteilten Befunden wurde bei dieser Untersuchung kein Beweis dafür gefunden, dass die Vitamin-B_{12}-Konzentration im Serum mit zunehmendem Alter abnimmt. Die angeführten Ergebnisse werden zusammen mit den von anderen Forschern mitgeteilten besprochen. Die biologische Bedeutung der Unterschiede zwischen den Vitamin-B_{12}-Spiegeln im Serum verschiedener hämatologisch normaler Individuen ist nicht klar.

Diversas edades y correspondientes niveles séricos de vitamina B_{12}.

Efectúose una investigación con respecto a la relación existente entre los niveles séricos de vitamina B_{12} y la edad y sexo de 242 sujetos hematológicamente normales de 0 a 82 años de edad. El contenido sérico de vitamina B_{12} fué determinado microbiológicamente por el uso de *Euglena gracilis* var. *bacillaris*. La escala de los valores séricos de vitamina B_{12} adoptó anchas extensiones en ambos sexos y en todas las edades. Las concentraciones séricas de vitamina B_{12} en los recién nacidos fueron significativamente más elevadas que las de las madres. Estas últimas a su vez presentaron menos vitamina B_{12} en el suero que las mujeres no embarazadas de misma edad. Los valores séricos más altos de vitamina B_{12} se encontraron en el grupo de personas de la 19 años de edad. Los hombres de 20 a 82 años presentaron una concentración sérica media de vitamina B_{12} más alta que las mujeres de misma edad. La diferencia fué significante. En contraste con los hallazgos de la mayoría de los demás investigadores, no hubo evidencia en esta investigación de una disminución de las concentraciones séricas de vitamina B_{12} a medida que subiera la edad. Discútense los resultados presentados aquí y los correspondientes a otras investigaciones. El significado biológico de las diferencias halladas entre los niveles séricos de vitamina B_{12} de los distintos grupos de sujetos hematológicamente normales, no se ha manifestado en forma ostensible.

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Red Blood Cell Survival in Cyanotic Congenital Heart Disease

by BENGT J. JONSSON

After a successful operation of a patient with tetralogy of Fallot, the polyglobulia and high hemoglobin concentration will be less pronounced or normalized. The hematological effect is analogous to that found when an individual, after acclimatization to high altitudes, returns to the sea level (5, 8, 9) and to the decrease of the red cell concentration during the neonatal period.

It has been discussed if the decrease in the red cell count is caused by an accelerated destruction or a decreased production of new cells. The iron turnover has been found to decrease markedly after a change from high altitudes to sea level (5, 8) but an increased hemolytic index has also been described (9). A normal red cell life span has been found after change from reduced barometric pressure to atmospherical pressure (2, 4). Signs of increased red cell destruction has however also been found (11). Following operation of patients with cyanotic congenital heart disease Josephs (6) found signs of decreased production as well as increased destruction of the red cells studied by means of the urobilin excretion.

The life span of red cells produced in hypoxia has been found to be normal. Lawrence *et al.* (7) found an iron turnover compatible with a normal survival of the red cells in two cases with cyanotic congenital heart disease. A normal life span studied by use of C^{14}-labeled glycine was found after acclimatization to high altitude in normal individuals (12) and in natives in high altitude (3). Animals exposed to reduced barometric pressure have a normal red cell life span (4, 11).

This study deals with the survival of the red cells from patients with cyanotic congenital heart disease transfused in individuals with normal oxygen saturation of arterial blood and also in one patient with hypoxia. Further the survival of normal cells transfused in patients with cyanotic congenital heart disease has been studied. In 4 cases the elimination of the red cells was followed after operation according to Blalock.

Methods

The life span of the red cells was determined with differential agglutination according to Ashby (1). The refined technique described by Young *et al.* (13) and Mollison (10) has, with minor modifications, been adapted in this study. The antisera used were anti-D and anti-A from the Institute of Forensic Chemistry in Stockholm and dried anti-M produced by Lederle. The anti-M serum was found to have a high agglutination power with less than 6400 unagglutinated cells per mm^3 in the four cases studied (nos. 1–4). Anti-D serum was used in one survival study (Fig. 7) and the numbers of unagglutinated cells were 35,000. Anti-A serum used in Cases 5 and 6 left respectively 14,200 and 36,000 cells unagglutinated.

The amount of blood transfused was so large that the concentration of the donor cells in the recipient the day after the transfusion was about 1 mill. per mm^3 except in Cases 2, 4 and 5 where the cell count was 646,000, 348,000 and 514,000 respectively. The number of transfused cells the day after the transfusion was taken as 100 % survival. For each estimation more than 2000 cells were counted. The same pipettes and counting chamber and the same lot of anti-serum were used throughout each survival study. In this material of small children with the most suitable veins damaged after catheterization and infusions there were often difficulties in collecting venous blood, and therefore skin-prick blood was drawn after a deep incision giving free bleeding. The error of the method was calculated from a series of samples taken in duplicate and was found to be ± 3.1 % including the error of bloodsampling, dilution, degree of agglutination and cell counting.

The normal blood was delivered from the blood bank and only fresh ACD-blood was used. The blood from the patients was sampled and controlled in the same way as ordinary donor-blood.

Material

The patients studied (Cases 1–7) were examined and treated at the Heart Unit of the Pediatric Clinic. The diagnosis and some findings are summarized in Table 1. Cases nos. 1–4 were operated according to Blalock. The "normal" recipients were children staying for a rather long time at the hospital. They had no signs of hemolysis, no anemia and no acute infection. The body weight did not change significantly during the study in any of the cases or recipients.

Recipient 1. O. E., boy, $1\frac{1}{2}$ years. Diabetes mellitus. Weight 11.4 kg.

Recipient 2. N. G., boy, $1\frac{4}{12}$ years. Eczema. Weight 11.8 kg.

Result

Normal blood transfused in patients with hypoxemia (Figs. 1–4)

The rate of elimination was normal both before and after the operation. A normal life span (120 days) was found. The sudden decrease in red cell count in connection with the operation corresponds to loss of blood during and a few days after the operation. Variation in the blood volume will also change the cell concentration but the blood volume was not determined. The marked variation in the cell count after operation in Case 4 (Fig. 4)

TABLE 1

Diagnosis and some findings in seven cases with cyanotic congenital heart disease

Case no.	Cath. no.	Age (years)	Sex	Body weight (kg)	Diagnosis	Hemoglobin, g%		Arterial oxygen sat., %	
						Before operation	>4 months after operation	Before operation	After operation
1	52	4	M	17.0	Tetralogy of Fallot	18.8	15.5	(deeply cyanotic)	85
2	228	8	M	19.6	Single ventricle + pulmonic stenosis	23.2	15.0	61	77
3	221	5	M	12.9	Tetralogy of Fallot	21.0	14.9	78	—
4	203	4	M	9.1	Tetralogy of Fallot	21.8	—	54	—
5	150	$2\frac{2}{12}$	F	9.4	Pseudotruncus	13.1		57	
6	162	4	M	16.1	Complete transposition of the great vessels + single ventricle + mitral atresia + atrial septal defect			73	
7	205	$\frac{8}{12}$	F	4.9	Single ventricle + mitral atresia + atrial septal defect	13.1		66	

might be explained by variation in blood volume. This patient developed heart failure and died 4 weeks following the operation. In Case 1 (Fig. 1) the first count of the transfused cells was made 4 hours after the operation. Thus the decrease cannot be caused by loss of blood during the operation but only by the bleedings the following days and the variation of blood volume. The decrease was less marked than in the other cases.

Blood from patients with hypoxia transfused in "normal" recipients (Figs. 5, 6)

The life span was found to be 60–80 days which is significantly shorter than normal. The slope of elimination is linear.

Blood from one patient with hypoxia transfused in another patient with hypoxia (Fig. 7)

The life span was shortened to the same extent as in the former group. The donor and the recipient had about the same degree of desaturation of the arterial blood.

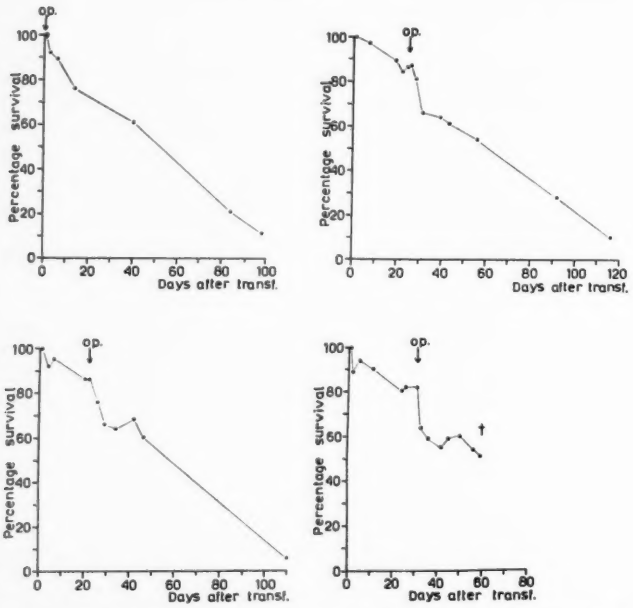


Fig. 1 (*top left*). Survival of normal red cells transfused in Case 1 in connection with the operation.

Fig. 2 (*top right*). Survival of normal red cells transfused in Case 2. Operation was performed 25 days after the transfusion.

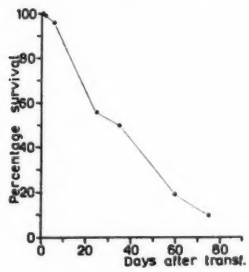
Fig. 3 (*bottom left*). Survival of normal red cells transfused in Case 3. Operation was performed 22 days after the transfusion.

Fig. 4 (*bottom right*). Survival of normal red cells transfused in Case 4. Operation was performed 31 days after the transfusion and the patient died 29 days later.

Discussion

The red cells produced by these patients with cyanotic congenital heart disease seems to be "faulty" as they are incapable of a normal survival. Whether this is caused by the chronic hypoxia cannot be concluded from the data available in this study. If the survival was found to be normal several months after the oxygen saturation of the arterial blood had increased, as a result of the operation, it might indicate that the hypoxia is the factor of importance. Such determinations have not been made. The decrease in life span was not marked but as these patients have a large amount of red cells the hemopoietic activity must be very high.

The decrease in red cell count after a successful operation of a patient with cyanotic heart disease seems to be caused by a decreased production of cells when the degree of hypoxia has become less marked. Normal red



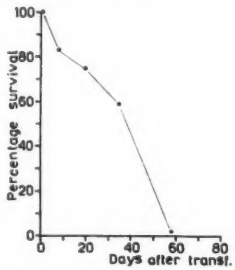


Fig. 5 (*left*). Survival of red cells from Case 5 transfused in Recipient 1.
Fig. 6 (*right*). Survival of red cells from Case 6 transfused in Recipient 2.

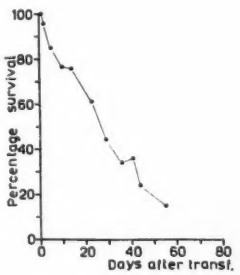


Fig. 7. Survival of red cells from Case 4 transfused in Case 7.

cells have a normal survival during the postoperative period. It is not probable that the sudden rise in the arterial oxygen saturation should increase the rate of destruction of the patients own cells. The life span of red cells from one cyanotic patient transfused into another cyanotic patient was found to be as low as in the two cases where the red cells were transfused in individuals with a normal arterial oxygen saturation. The increased excretion of urobilin after operation which Josephs (6) found might have been caused by hemolysis of blood in the thoracic cavity and not by an increased destruction of the blood in the vascular system.

Summary

The red cells from patients with cyanotic congenital heart disease were found to have a shorter life span than normal. Red cells from normal individuals transfused in the cyanotic patients survived normally both before and after an operation giving increased arterial oxygen saturation.

Survivance des érythrocytes dans la cardiopathie congénitale cyanotique.

Les érythrocytes des malades atteints de cardiopathie congénitale cyanotique ont une durée de vie au-dessous de la normale. Les érythrocytes des individus normaux transfusés à des cyanotiques survivent normalement à la fois avant et après une opération qui permet d'augmenter la saturation en oxygène des artères.

Überleben roter Blutkörperchen in kongenitaler cyanotischer Herzerkrankung.

Es wurde gefunden, dass rote Blutkörperchen von Kranken mit angeborener cyanotischer Herzkrankheit eine kürzere Lebensspanne haben als normale Zellen. Rote Blutzellen von normalen Individuen, die auf cyanotische Kranke übertragen wurden, verblieben in normaler Weise am Leben bevor und nach einer Operation, die eine vergrösserte Sauerstoffsättigung im arteriellen Blut herbeiführte.

Sobrevivencia de los glóbulos rojos en la cianosis cardíaca congénita.

Ha sido observado que en los pacientes afectos de cianosis cardíaca congénita la longevidad de los glóbulos rojos es inferior a lo normal. Los glóbulos rojos, provenientes de indivíduos normales, transfundidos en los pacientes cianóticos, sobrevivieron normalmente tanto pre como postoperatoriamente, proveyendo una saturación oxígeno-arterial acrecentada.

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A Wilms' Tumour Family

by TORBJØRN STRØM

Familial occurrence of Wilms' tumour is not frequent (see e.g. Harrah). Although renal tumours may occur in two or more siblings, heredity is not a direct factor (Campbell).

In 1955, Fitzgerald & Hardin went through the literature and only found the following 5 reports of familial Wilms' tumour:

(*a*) Walker, in his analysis of 138 cases reported one in which a brother "was supposed to be similarly affected".

(*b*) A case is credited to Strümpel where 2 brothers were affected.

(*c*) Deuticke had a case which was not operated on. The patient had a 2½ year old brother who "died of the same condition".

(*d*) Three cases of Wilms' tumour in one family were reported by Bobbio. One case was proven; the diagnosis was clinical in the other two.

(*e*) Marlow reported 4 cases, 2 brothers and 2 sisters in the same family who had Wilms' tumours. Three of his 4 cases were proven pathologically.

In addition, there is the family observed by Fitzgerald & Hardin in which a father and 2 of his 3 children were operated on for Wilms' tumour. The diagnosis was verified microscopically in the children. They assume that this is the first instance reported with Wilms' tumour in both progenitor and offspring.

In the above families the diagnosis of Wilms' tumour was made histologically in more than one case only in the following instances: 3 of Marlow's 4 cases, and 2 of Fitzgerald & Hardin's 3 cases.

Renal tumours are considered to be the second commonest type of malignant tumour and the most common type of abdominal malignant tumour in infants and small children (Campbell, Dean, Gérard-Marchant, Schweisguth). Further, renal tumours in the young are practically all embryonic (Wilms') (Campbell, Dean). It is probable from the case histories that a Wilms' tumour was present in all the above cases.

Case History

In 1956, an 11-month-old boy was admitted to "Sanitetsforeningens" Hospital in Mo, with a large tumour in the left side of the abdomen. It was stated that other children in the family had died from a similar disease. The tumour was diagnosed as a

renal tumour and the patient operated on. Pathological diagnosis: Embryonic malignant renal tumour (Wilms' tumour).

In the patient's family the following cases of malignant tumour were found:

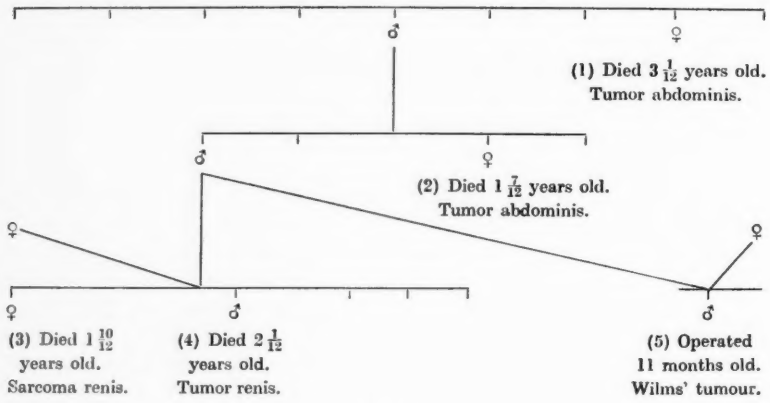

Fig. 1.

(1) Girl, born 12/5 1872, died 20/6 1875, aged 3 years and 1 month. Cause of death: abdominal growth.

(2) Girl, born 27/8 1899, died 23/4 1901, aged 1 year and 7 months. Cause of death: abdominal growth. Relatives think they remember that she had a large tumour in one side of the abdomen.

(3) Girl, born 9/10 1915, died 7/9 1917, aged 1 year and 10 months. Clinical diagnosis: sarcoma renis. Considered inoperable.

(4) Boy, born 4/7 1918, died 23/8 1920, aged 2 years and 1 month. Clinical diagnosis: tumor renis. Operation not performed because of bad prognosis.

(5) Boy, born 22/4 1955, operated on when 11 months old. Pathological diagnosis: embryonic malignant renal tumour (Wilms' tumour).

In this family, in 3 generations there were 5 children who died or were operated on for abdominal tumour between the ages 1–3 years. Three of these cases were siblings in the last generation. In each of these three cases the diagnosis was renal tumour. One was operated and the diagnosis verified as Wilms' tumour. In the other two cases operations were not performed, and a more exact diagnosis could not be made. But as renal tumour is the most common type of abdominal malignant tumour in this age group, and as practically all such tumours are Wilms' tumours, it can be presumed that Wilms' tumour was present in all these cases.

No other cases of malignant tumour were found in this family. This is

another reason for supposing that the same type of tumour was present in all these cases.

It is evident from the figure that Case 5 had a different mother from Cases 3 and 4. This mother previously had a healthy child, 8 years of age.

It is probable that in this family there is a hereditary predisposition to Wilms' tumour which has attained a rather high penetrance in the father of Cases 3, 4 and 5.

Summary

A family is described in which, in the course of 3 generations, 4 children died and one was operated on between the ages of 1–3 years with a diagnosis of renal or abdominal tumour (see Fig. 1). In one case the diagnosis of Wilms' tumour was verified, in two cases the clinical diagnosis was renal tumour and in two cases, abdominal tumour. Various points are mentioned which indicate that Wilms' tumour was present in all the cases and that this family has a hereditary predisposition to this tumour.

Famille avec tumeur de Wilms.

Description d'une famille dont, au cours de 3 générations, 4 enfants moururent et un fut opéré entre un et trois ans avec un diagnostic de tumeur rénale ou abdominale. Dans un cas, le diagnostic de tumeur de Wilms fut vérifié; dans deux cas, le diagnostic clinique établit une tumeur rénale et dans les deux autres une tumeur abdominale. D'autres détails cités indiquent la présence d'une tumeur de Wilms dans tous les cas et la prédisposition héréditaire de cette famille à cette tumeur.

Eine Familie mit Wilmsschen Tumor.

Es wird eine Familie beschrieben, in welcher durch drei Generationen hindurch 4 Kinder im Alter von 1–3 Jahren starben und eines operiert wurde mit der Diagnose eines renalen oder abdominalen Tumors. In einem Fall wurde die Diagnose eines Wilmsschen Tumors bestätigt, in drei Fällen war die klinische Diagnose die eines Nierentumors und in zweien die eines Bauchtumors. Verschiedene Momente, welche darauf hinweisen, dass es sich in allen diesen Fällen um einen Wilmsschen Tumor handelte und dass diese Familie eine erbliche Veranlagung zu diesem Tumor besitzt, werden angeführt.

Tumor familiar de Wilms.

Descríbese el caso de una familia en la que durante el transcurso de 3 generaciones, entre 1 y 3 años de edad murieron 4 niños, siendo operado otro, con diagnóstico de tumor renal o abdominal. En un caso fué comprobado el diagnóstico de tumor de Wilms; en dos casos la diagnosis clínica fué tumor renal y en dos casos tumor abdominal. Menciónanse varios puntos que indican la existencia del tumor de Wilms en todos los casos y que esta familia presentaba predisposición hereditaria al tumor en cuestión.

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Surgical Treatment of Funnel Chest

by GUNNAR EKSTRÖM and OVE QVIST

Since 1952 the operation for funnel chest described in this paper has been employed at Kronprinsessan Lovisas Barnsjukhus (KLB). The indications for surgery and the experience from 40 consecutive cases will now be discussed.

Funnel chest usually is detected in early infancy, but as a rule the deformity at that stage is slight or moderate. In the following years it may remain slight and require no treatment, or it may progress so that correction is indicated.

Dysphnoea, fatigability, susceptibility to respiratory infections, and cough were reported in one-third of the patients operated on at KLB.

The deformity consists of a more or less deep, funnel-shaped depression of the caudal portion of the sternum. A measure of the depression is the distance between the spine and the sternum at its deepest lying point. Paradoxical respiration with shortening of this distance during inspiration, instead of the normal lengthening, was present in more than half of our patients.

A systolic murmur was registered stethoscopically and phonocardiographically in about two-thirds of the series. Electrocardiographic signs of intraventricular conduction defect were more common than usual; changes produced by abnormal position of the heart were also registered. Two-thirds of the patients had cardiac dislocation, usually to the left, or other positional or configurational cardiac changes.

Spirometry in children (Engström *et al.*, 1956) and adults (Hansen & Jacoby, 1956) with funnel chest not infrequently shows some deviation from normal respiratory function. In a relatively large number of our patients tests of cardiac function revealed impaired physical capacity; exercise tolerance tests were made with the bicycle ergometer (Sjöstrand, 1953). Cardiac catheterization and angiocardiography in some of the children with considerable thoracic deformity showed hypertension, especially in the right auricle, and decelerated pulmonary circulation. Similar

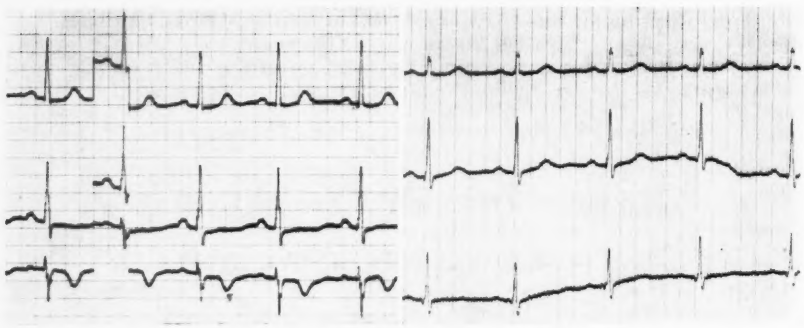

Fig. 1. Electrocardiogram, A.-M. B., female, aged 6 years. *Left:* Before operation, left axis deviation. *Right:* After operation, normal tracings.

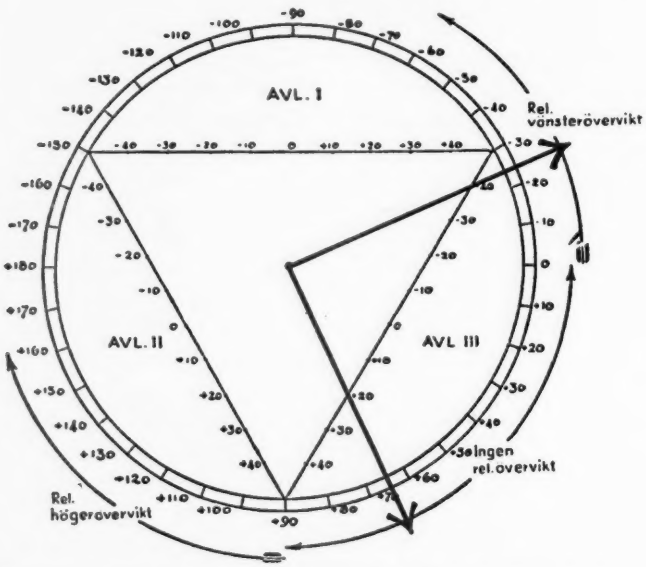

Fig. 2. Electrocardiogram, A.-M. B., female, aged 6 years, before and after operation. Schematic presentation of postoperatively normalized left axis deviation.

findings were described by Gyllenswärd (1955) and Dorner *et al.* (1950). These changes reflect the compression which the sternum exerts on the conus arteriosus.

Many of the older children in our series had kyphosis. This complication is also common in adolescents and adults with funnel chest (Wulff, 1956).

The following are the indications we accept for surgical treatment:

Fig. 3. 10-year-old girl before and one year after operation. Note the preoperative kyphosis and forward shoulder displacement.

(1) Signs of respiratory and/or circulatory disturbance.
(2) Sternal depression of a severity implying risk of future spinal deformity.
(3) Strong cosmetic reasons. A child, and probably also an adult, prefers a scar on the chest to a deep and easily detectable depression.

The first operation for funnel chest at KLB was performed by Sandblom in 1948. Fifty children have now been treated, the first ten according to the methods of Brown (1951), Lester (1950) or Ravitch (1951). In the 40 children operated on since 1952, another method has been used.

In this operation the sternum is freed by total or partial subperichondrial resection bilaterally of the costal cartilages involved in the funnel, usually the third to the seventh. When the xiphoid process has been liberated and the lower ligamentous attachments of the sternum divided, the sternum is freed from the pericardium and pleurae by blunt dissection and is lifted forward. Pleural trauma may occur during this manœuvre, but can generally be avoided. The sternum is further mobilized by a transverse wedge osteotomy just below the gladiomanubrial junction. The periosteum at the

edges of the wedge on the anterior sternal surface is sutured with strong material and the depression is thereby corrected. Further support is provided by a rib slung transversely behind the sternum and fixed to it with steel wire (cf. Wahren, 1950). This rib strut is obtained from the bone bank and is free from periosteum. It is absorbed within a few months, during which time costal cartilage is regenerated in corrected position. None of our patients developed osteitis or necrosis of the sternum. In one patient the rib strut was not absorbed and had to be removed after a year. Inspection showed that it had not been freed from periosteum.

The ages of the children ranged from 6 months to 15 years. The most favourable results were obtained in children treated before school age. The operation was also most easily performed then. About 2 weeks' hospitalization was required as a rule, with the first week in bed. Physiotherapy was given when indicated, particularly to the older children.

At follow-up examination, at least 6 months after the operation, subjectively improved physical capacity was reported by most patients. All were satisfied with the cosmetic result. Keloids occasionally appeared in the wound. The sagittal depth of the thorax increased considerably and the configuration and position of the heart were normalized. The children's posture was also improved. About three-quarters of the series had preoperatively had signs of respiratory or circulatory disturbance. In half of these patients the disturbance was eliminated by the operation and in the others there was improvement of varying degree. There were no deaths in the series and no important complications.

Summary

A surgical technique for the correction of funnel chest is described. The operation has been performed on 40 children without fatality.

Funnel chest is not only a cosmetic defect. All cases detected in infancy should be regularly examined. The most suitable age for the operation described is 3 to 6 years.

Traitement chirurgical du thorax en entonnoir.

Description d'une technique chirurgicale pour la correction du thorax en entonnoir. 40 enfants ont subi cette opération; il n'y a pas eu de mort. Le thorax en entonnoir n'est pas seulement un défaut cosmétique. Tous les cas dépistés pendant la première enfance doivent être examinés régulièrement. Le meilleur âge pour opérer est entre 3 et 6 ans.

Chirurgische Behandlung der Trichterbrust.

Es wird eine chirurgische Technik für die Korrektur der Trichterbrust beschrieben. Die Operation wurde an 40 Kindern ohne einen Todesfall durchgeführt. Die Trichter-

brust ist nicht nur ein Schönheitsfehler. Alle in früher Kindheit entdeckten Fälle müssen regelmässig untersucht werden. Das für den beschriebenen Eingriff günstigste Alter ist von 3–6 Jahren.

Tratamiento quirúrgico del torax en embudo.

Descríbese una técnica quirúrgica para la corrección del tórax infundibuliforme. La operación fué ejecutada en 40 niños sin desenlace fatal. El tórax en embudo no es un defecto cosmético solamente. Todos los casos identificados en la infancia deben examinarse con regularidad. La edad más adecuada para la operación descrita es la de 3 a 6 años.

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The Correlation between the Development of the Hypophysial Portal System and the Onset of Neurosecretory Activity in the Human Fetus and Infant

by NIELS RÄIHÄ and LARS HJELT

Introduction

Since the first observations on the existence of the hypothalamo-hypophysial portal circulation in man by Popa & Fielding (1930, 1933) and Wislocki (1938), these vessels have been extensively studied by numerous workers. The hypophysial portal circulation seems to be a constant finding in all species so far investigated (Green, 1951). Harris (1944) was the first to mention the possibility that this morphological peculiarity might bear significance for the anterior pituitary function.

Xuereb, Prichard & Daniel (1954) have made accurate studies of the hypophysial portal circulation in man. Branches from the superior hypophysial arteries supply a rich vascular plexus situated in the pars tuberalis of the adenohypophysis. This plexus gives rise to numerous capillary loops or tufts which enter the tissue of the median eminence of the tuber cinereum. These loops are referred to as the "primary plexus" of the hypophysial portal vessels. The blood from the primary plexus drains into the large portal trunks mainly situated on the ventral surface of the pituitary stalk in the pars tuberalis. The portal trunks break up to distribute their blood into the sinusoids of the pars distalis called the "secondary plexus".

The development of the hypophysial portal circulation has been studied by d'Espinasse (1933) and by Niemineva (1950), but otherwise the literature on the ontogenesis of the pituitary portal circulation is scanty. Using a benzidine staining method, Niemineva found that the capillary loops of the primary plexus commence during the middle of the fetal period, being fully developed at term.

"Neurosecretory" material has been observed to appear in the hypothalamus of dog fetuses about one week before birth (Scharrer & Scharrer,

1954). Neurosecretory granules appear in the chick embryo in the cells of the hypothalamic nuclei on the 13th or 14th day of incubation (Wingstrand, 1954). In their studies on the formation of antidiuretic hormone in the hypothalamus, Benirschke & McKey (1953) have found neurosecretory granules stainable with chrome-hematoxylin in the human fetus during the 20th week of gestation.

In the present investigation the development of the primary plexus of the hypophysial portal circulation is studied in human fetuses, infants and children, with special reference to the onset of neurosecretory activity.

Materials, Methods and Results

The material consists of the hypothalamic regions and pituitaries of 7 human fetuses obtained from therapeutic and spontaneous abortions. The weights of the fetuses range between 65 and 730 g. The remainder of the material consists of 40 prematures, infants and children, the weights ranging between 800 g and 33 kg, obtained from routine autopsies at the Children's Clinic of the University of Helsinki. The cause of death in these newborn, infants and children varied greatly, but none was likely to have directly involved the hypothalamic-pituitary system.

The heads of the fetuses from the therapeutic abortions were fixed in Zenker's or Bouin's fluid within a few minutes after the operation. In all other cases Zenker's fluid was perfused through the carotid arteries within 4 to 24 hours after death. The hypothalamic regions and pituitaries were dissected free, fixed and imbedded in paraffin.

Serial sections of 7 to 20 μ thickness were stained according to the chrome-hematoxylin phloxin method of Gomori (1941) as recommended by Bargmann (1949).

The development of the capillary loops of the primary plexus from the pars tuberalis into the nervous tissue of the median eminence is seen in Figs. 1 to 4.

Chrome-hematoxylin positive neurosecretory material was first observed in the median eminence of a fetus weighing 800 g (Fig. 2). The stainable material consisted of fields of fine secretory granulation near the developing capillary loops of the primary plexus. In fetuses with increased weights the appearance of neurosecretory material was consistent. The amount of neurosecretory material, the density and the size of the granules increased after birth (Figs. 7 and 8). Neurosecretory material was found in some of the sections along the walls of the capillaries of the primary plexus, as seen in Figs. 5, 7 and 8. Fig. 5 shows Gomori positive material within a portal vessel of the pars tuberalis.

Discussion

Adams & Sloper (1956) using a performic-acid alcain blue reaction for cystine have conclusively demonstrated that the Gomori positive material

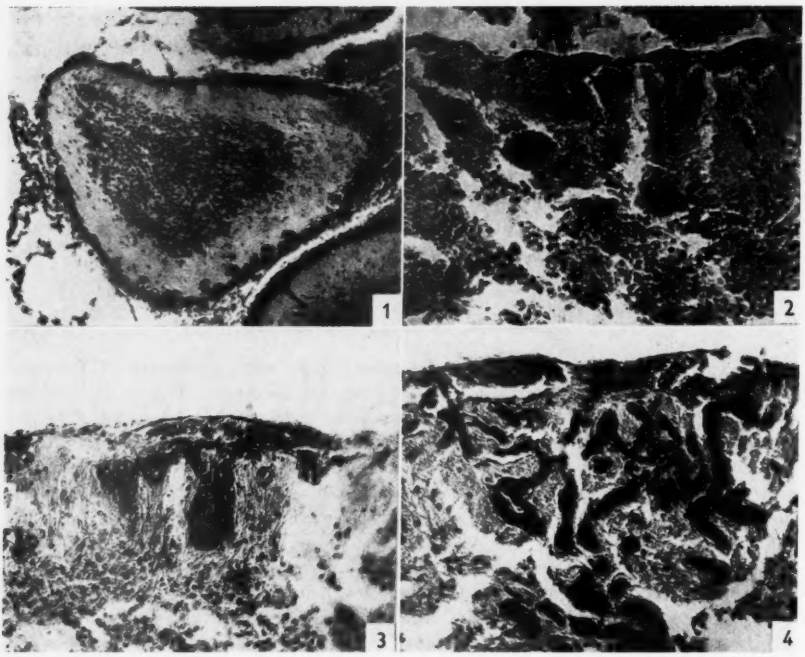

Fig. 1. Cross section of the hypophysial stalk of a human fetus weighing 500 g. Small capillary buds penetrating from the pars tuberalis into the nervous tissue of the median eminence are seen. Magnification × 120. Thickness of section 20 μ. Gomori's chrome-hematoxylin phloxin stain.

Fig. 2. Horizontal section of the hypophysial stalk of a human fetus weighing 800 g. Developing capillary buds are seen. Fields of finely granulated neurosecretory material to the left. Magnification × 160. Thickness of section 10 μ. Gomori's chrome-hematoxylin phloxin stain.

Fig. 3. Horizontal section of the hypophysial stalk of a human newborn infant weighing 2400 g. A capillary loop is seen which penetrates into the median eminence and runs back into a portal vessel of the pars tuberalis. Magnification × 160. Thickness of section 10 μ. Gomori's chrome-hematoxylin phloxin stain.

Fig. 4. Horizontal section of the hypophysial stalk of an 8-month-old human infant weighing 7300 g. Magnification × 160. Thickness of section 10 μ. Gomori's chrome-hematoxylin phloxin stain.

in the hypothalamus of man, rat and dog contains posterior lobe principles rich in cystine. On the other hand Saffran *et al.* (1955) have shown that posterior pituitary extracts contain as an impurity a factor which causes the release of ACTH from the anterior pituitary *in vitro*. The Gomori positive neurosecretory material may hence contain anterior lobe stimulating agents in addition to the posterior lobe principles present. Porter and co-workers at the Southwestern Medical School of the University of

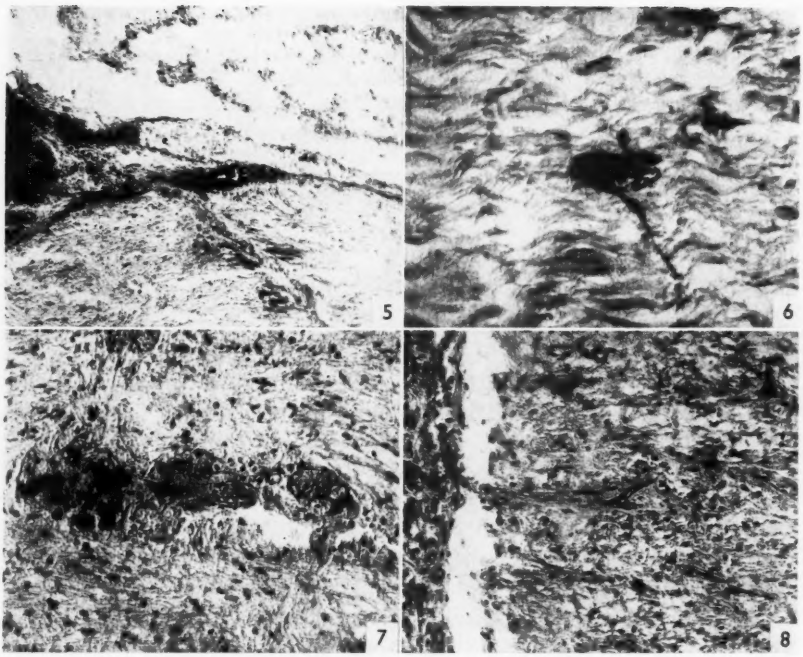

Fig. 5. Horizontal section of the hypophysial stalk at the junction between pars distalis, pars tuberalis and the infundibular process of a 10-day-old human infant weighing 4200 g. A capillary tuft surrounded by neurosecretory granules is seen. Neurosecretory material is also seen within a portal vessel of the pars tuberalis. Magnification × 160. Thickness of section 15 μ. Gomori's chrome-hematoxylin phloxin stain.

Fig. 6. Nerve cell in the tuber cinereum of an infant with the age of 1 year, weighing 8220 gr. The cell and the axone contain Gomori positive neurosecretory material. Magnification × 250.

Fig. 7. Neurosecretory material near the capillary tufts of the primary plexus. Human infant weighing 9500 g and aged 1 year 7 months. Magnification × 260. Thickness of section 7 μ. Gomori's chrome-hematoxylin phloxin stain.

Fig. 8. Neurosecretory material along the wall of a capillary tuft of the primary plexus. Pars distalis seen to the left. Human infant weighing 33 kg, 10½ years old. Magnification × 260. Thickness of section 7 μ. Gomori's chrome-hematoxylin phloxin stain.

Texas recently announced the isolation of a new neurohumoral agent, obtained from the hypophyseal portal blood of hypophysectomized dogs which stimulated the release of ACTH from the anterior pituitary.

These separate observations strongly support the hypothesis, that some agent or agents are released from the nerve cells of the hypothalamic centers, passed down to the median eminence, into the capillary loops of the primary plexus via nerve axones and further through the portal circulation

TABLE.

Volume of blood-filled capillaries in the infundibular process per cu.mm tissue in fetuses of different weight classes (Niemineva).

Fetal weight in g	Volume in cu.mm of capillaries in cu.mm tissue
120	0.0042
800	0.0044
1510	0.0126
2730	0.0192

to the anterior pituitary where they regulate the activity of the gland. They also explain the well known correlation between posterior and anterior lobe hormones (Scharrer, 1954).

The hypophysial portal circulation and the possible neurosecretory agents released into the vessels of the primary plexus may hence form a connecting link between the external environment and the endocrine target organs of the body. The question may well be asked: At what stage in the human development does this mechanism mature?

The results of our investigation are in close agreement with those of Niemineva as seen in the Table. This investigator observed a rapid increase in the volume of the blood-filled capillaries in the infundibular process of human fetuses weighing between 800 and 1500 g. It is interesting to note the correlation between the maturation of the vascular connection between the anterior pituitary and the nervous tissue of the median eminence and the first appearance of neurosecretory material.

In his excellent experimental studies on the role of the pituitary in the fetal development Jost (1953, 1954) concludes that the hypophysial impulse apparently is not required for the growth and differentiation of the fetal endocrine glands, but in the absence of the hypophysis the physiological activities of the glands remain low and inefficient. Furthermore, Jost concludes on the basis of his experimental studies that the anterior pituitary activity starts towards the end of the intrauterine life in rabbits and rats.

On the basis of the above mentioned histological and experimental observations it seems likely that the complex mechanism whereby the endocrine glands are affected by environmental changes does not mature until fairly late in fetal life.

Jailer (1950) and Jailer, Wong & Engle (1951) found that newborn rats and premature human infants do not respond to injections of adrenaline

with a discharge of ACTH, whereas full-term infants and 8-day-old rats do respond.

The state of development of the hypothalamo-hypophysial connecting mechanism seems hence to be an important factor in the reactions of newborn infants to the stresses and strains of birth.

Acknowledgements

This work was made possible by a grant from the Signe and Ane Gyllenberg Foundation which we gratefully acknowledge. We also extend our thanks to the Association for the Aid of Crippled Children for their interest in our investigation.

Summary

The development of the primary plexus of the hypophysial portal vessel circulation was studied in human fetuses, prematures, infants and children, with special reference to the onset of neurosecretory activity.

A close correlation was observed to exist between the state of development of the capillary loops of the primary plexus and the onset of microscopically visible neurosecretory activity.

Correlation entre la circulation de la porte de l'hypophyse et le début de l'activité neuro-sécrétoire chez le fœtus et le nourrisson.

Le développement du plexus primaire de la circulation de la porte de l'hypophyse a été étudié sur des fœtus, des prématurés, des nourrissons et des enfants, en rapport avec le début de l'activité neuro-sécrétoire. Il est apparu qu'il existe une corrélation étroite entre la formation des anses capillaires du plexus primaire et le début de l'activité neuro-sécrétoire visible au microscope.

Die Wechselbeziehung zwischen der Entwicklung des hypophysären Pfortadersystems und dem Anfang von neurosekretorischer Aktivität beim menschlichen Fötus und Kinde.

Die Entwicklung des primären Plexus des hypophysären Pfortaderkreislaufes wurde bei menschlichen Föten, vorzeitigen Neugeborenen, Säuglingen und Kindern mit spezieller Berücksichtigung des Beginns von neurosekretorischer Tätigkeit studiert. Eine enge Wechselbeziehung wurde zwischen dem Entwicklungszustand der Kapillarschlingen des primären Plexus und dem Beginn von mikroskopisch sichtbarer neurosekretorischer Tätigkeit beobachtet.

Correlación entre el desarrollo del sistema portal hipofisario y comienzo de la actividad neurosecretoria en el feto e infante humanos.

El desarrollo del plexo primario de la circulación portal hipofisaria fué estudiado en fetos humanos, prematuros, infantes y niños, con referencia especial al comienzo de la actividad neurosecretoria. Se observó una íntima correlación entre el estado de desarrollo ansocapilar del plexo primario y el comienzo microscópicamente visible de la actividad neurosecretoria.

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Infantile Cerebral Palsy. A Sociomedical Enquiry Carried out in the County of Østfold in Norway 1954—1955

by BJARNE ANDERSEN

(Summary of Supplement 109)

A definition of the term infantile cerebral palsy is given, and attention is drawn to the various conditions which must not be confused with it. It is emphasized that cerebral palsy is not a disease entity, but a group of conditions resulting from brain injuries. These conditions are grouped together for practical therapeutic purposes.

The development of therapy for cerebral palsy children is described briefly, and an outline is given of the problems to be discussed in this paper.

In enquiring into the incidence of infantile cerebral palsy in the County of Østfold, Norway, the author has found 84 cases under the age of 21. Seventy-seven of these have formed the nucleus for a study of various aspects of this condition.

The geographical distribution of cases in the County is examined, together with their distribution according to age.

It is calculated that on an average 3.6 infants are born annually per 100,000 inhabitants in the County, which means that there are approximately 1.9 cases of cerebral palsy per 1000 births. The condition seems to occur considerably less frequently in Europe than in the U.S.A.

Assuming that the figures for Østfold are representative of Norway as a whole, the following estimate is obtained: 119 children are born with cerebral palsy in Norway each year.

The number of cases of an age suitable for treatment (under 21) is judged to be either 1500 or 2300, according to whether calculations are based on the total number of cases found in Østfold, or on the 5–9 age-group.

It is the duty of doctors to report all cases, but this has very seldom been done. As a result, only a few of the cases have been registered.

The case material is divided into the usual clinical types, and their distribution tallies almost exactly with the results of corresponding enquiries in the U.S.A. (Pohl).

As to the degree of severity of the cases, not quite half were moderately involved, a fourth were severe, and a third were mild cases.

The various circumstances that may have caused patients to have cerebral

palsy, or which are assumed to be the cause of it in some cases, were investigated. The cases are divided into categories according to the time, in relation to birth, when the injury is thought to have occurred.

The various conditions which may accompany cerebral palsy and complicate treatment are listed. An estimate of the patients' intelligence is given: more than half (60 per cent) were assumed to be of about normal intelligence. Their speech ability is shown. Somewhat more than half (57 per cent) had speech defects. Epilepsy was present in the anamnesis of $\frac{1}{3}$ of all cases. Visual disorders occurred in 17 cases (22 per cent) and auditory disorders in only one case.

First the types of treatment which are believed to be necessary for all the patients in Østfold are described, and then compared with the extent to which such types of treatment have been given. The need for various forms of in-patient treatment is discussed. This is compared with the number of cases receiving needed treatment as in-patients.

Most children of school age with cerebral palsy in the County of Østfold receive the schooling they are entitled to as long as they are mentally and physically capable of it. They usually attend ordinary schools, and are seldom taught at home. However, more than half of these children attending ordinary schools have difficulty in keeping up (13 out of 20) and must be assumed to be in need of a special school.

The number of young people needing help with vocational training was small; 4 out of 7 patients had decided on their future occupations and were able to obtain training.

Enumerations are given of the expenses incurred by the State and local authorities, insurance companies, and parents or guardians for the patients' treatment in 1954. Total expenses (not including those connected with mental defectives) amounted to about 50,000 kroner (approximately $7143). Complete treatment for every patient in the county would cost approximately 250,000 kroner (approximately $36,000).

The incomes of most parents or guardians in 1954 were between kr. 8000 and kr. 12,000 (approximately $1142 and 1700). In most cases their expenses were under kr. 1000 (approximately $142), and in 39 per cent of cases the parents had no extra expenses on account of the child's disability. In most cases (35.5 per cent) the parents "or guardians" occupation was in trade and industry.

In 19 cases the child with cerebral palsy was an only child, and in 56 cases there were between two and twelve children in the family.

On the basis of this study of cerebral palsy in the County of Østfold a number of suggestions are made in respect to the work to be done in future for prevention, therapy and program administration.

Acta Pædiatrica **46**: 619—620. Nov. 1957

From the Department of Medical Physics, Karolinska Institutet, Stockholm, Sweden

Biophysical Analyses of the Formation and Structure of Human Fetal Bone

A Microradiographic and X-ray Crystallographic Study

by GÖRAN WALLGREN

(Summary of Supplement 113)

The recent development and application of biophysical methods of analysis, capable of providing detailed information regarding the submicroscopic structural and chemical characteristics of biological materials, has been of particular value in the study of bone, and has led to our current concept of this tissue as a dynamic and extremely important physiological system. To a great extent, however, such investigations of bone have been confined to the adult tissue, and thus far have provided only a partial insight into the ultrastructural details of bone formation and growth.

The present investigation, therefore, has been undertaken in an effort to increase our knowledge regarding the structural and functional aspects of rapidly growing bone. Experimental emphasis has been placed primarily on quantitative and ultrastructural analyses of the mineral compartment, although additional information has been sought regarding the relationship of bone mineral to the underlying matrix.

The techniques employed habe been those of quantitative microradiography, which measures the total mineral content in microscopic structures of bone, and of X-ray microdiffraction, which provides information relating to the crystalline and chemical nature of the bone mineral and to is physical orientation in the tissue. Details regarding the structure and orientation of the organic matrix have been investigated by means of polarization microscopy and X-ray diffraction methods.

The experimental objects employed in this study have been human fetal femurs, taken from fetuses ranging in age from 6.5 weeks to full-term. The choice of fetal bone has been based on the assumption that those changes in ultrastructure which are characteristic of all bones during rapid growth would be most evident at a time when the growth rate of the entire body is at its maximum. Moreover, it was hoped that the use of this material would also permit supplementary observations to be made on some of the

specific details of human fetal bone formation and growth, our knowledge of which is rather limited.

This investigation has allowed the following conclusions regarding the formation and growth of human fetal bone to be drawn:

1. Newly-formed bone in the fetal femur possesses a very low degree of mineralization. From its very first appearance, however, the mineral component of this bone exhibits an X-ray diffraction pattern characteristic of calcium-hydroxy-apatite.

2. The mineral content of fetal bone increases rapidly during the three weeks immediately following its first appearance, but thereafter maintains an almost constant level up to the time of birth. The linear absorption coefficient, which reflects the degree of mineralization, has a value of approximately 85 in nearly all mature fetal bone, as compared with a figure for adult bone of about 95. However, certain portions of the fetal bone, i.e., the calcified cartilage cores of endochondral bone, the central cores of the periosteal bone layers, and the innermost portion of the primary periosteal collar (Grenzlinie), possess a higher degree of mineralization then does even adult bone, their linear absorption coefficient attaining a value of about 100.

3. Parallel to the rapid increase in mineral content in fetal bone, there occurs an increase in the long dimension of the apatite crystallites, which in newly-formed bone is very small. In full-term fetuses, this dimension averages 220 Å, which is approximately the same as the average value for adult bone. In fetal samples whose average age is 15 weeks, on the other hand, the crystallite long dimension averages approximately 160 Å. The initial increase in crystallite size appears to be very rapid, and its rate is strikingly similar to that of the increase in mineral content.

4. The first crystallites formed in fetal bone, are not oriented with respect to the underlying collagenous matrix. Between one and two weeks after the appearance of the crystallites, however, they exhibit a distinct orientation in the long axis of the collagen fiber bundles. The factors which determine the crystallite orientation seem to be related to the organic matrix rather than to the crystallites themselves.

5. At the ultrastructural level of organization, the rapid and progressive increase in the degree of mineralization of fetal bone seems to be related primarily to the increase in size of the small apatite crystallites during bone growth. The rate of increase in mineral content thus appears to be a function of the rate of increase in crystallite size, while the ultimate level of mineralization attained in a given ultrastructural area of fetal bone is governed by those factors which cause crystallite growth to cease. These latter factors appear to be properties of the organic matrix rather than of the crystallites, and their nature is not yet understood.

Acta Pædiatrica **46**: 621—627. Nov. 1957.

Immunization Against Whooping Cough

Discussion at the Meeting March 13, 1957, of the Danish Paediatric Society

Introduction

J. Ørskov, Director of the State Serum Institute, Copenhagen: It was pointed out that at the State Serum Institute the problems as yet unsolved concerning whooping cough vaccination were being considered, and Director Ørskov wished to discuss the subject with paediatricians. The relevant facts concerning whooping cough vaccination and its effects would be presented. The various possibilities for an immunization programme were sketched as it was considered desirable to discuss the question thoroughly with paediatricians in order to obtain an arrangement best adaptable to the prevailing conditions in Denmark.

Some considerations regarding the possible use of triple vaccine (diptheria-tetanus-pertussis) in Denmark

I. Scheibel, Departmental Chief at the State Serum Institute: Before a decision is made as to what extent more extensive whooping cough vaccination should be associated with diphtheria-tetanus vaccination in the employment of a triple vaccine, the advantages and disadvantages of such a triple vaccination should be thoroughly considered. A few points were emphasized: The first concerned which vaccine should be preferred, and the second to what extent the intervals which are considered optimal for vaccination against the three diseases fit in with one another.

There are two types of triple vaccine; the one consists of diphtheria and tetanus toxoid and whooping cough bacteria, and the other contains, in addition, a precipitating or adsorbing chemical substance, as a rule, an aluminium compound.

The first type is stated to give fewer local reactions than the adsorbing type, while the general reactions are said to be similar for both types. It has been postulated from various quarters that the adsorbing and re-

sorption delaying chemical substance could be omitted when whooping cough bacteria were added to the diphtheria-tetanus vaccine, as these should produce the same increase of effect of the toxoids as is obtained by $Al(OH)_3$ or similar substances.

The results are, however, far from uniform. In the course of the past year therefore, experiments on guinea-pigs were undertaken to investigate the effect of the 2 types of Danish triple vaccine compared with the effect of the ordinary diphtheria-tetanus vaccine.

The results of such an experiment appear from Table 1.

It will be observed that whooping cough bacteria cannot replace $Al(OH)_3$ but also that admixture of whooping cough bacteria to the ordinary diphtheria-tetanus vaccine implies an increase in the effect of the vaccination where both antigens are concerned.

As regards the whooping cough component, Miss Kragh Andersen found, in experiments for the protection of mice, no difference in the effect of the 2 types of vaccine nor when comparison was made with pure whooping cough vaccine.

The conclusion must be that the adsorbing vaccine type should be chosen in view of diphtheria-tetanus immunity if the employment of the triple vaccine in Denmark is desired even although local reactions are perhaps slightly more frequent, a subject concerning which there is not full unanimity.

It may be mentioned that Barr and co-workers employing a type of vaccine similar to that of the proposed Danish type found up to 80 per cent local reactions with 8.5 per cent sterile abscesses in infants who were vaccinated at the ages of 1 week, 6 weeks and 14 weeks, while Miller and coworkers in San Francisco observed only insignificant side-reactions with a similar vaccine. Here the injections were preferably administered intramuscularly or deeply subcutaneously in the thigh or the arm, and in an investigation of 172 children, the majority between 6 and 12 months, no sterile abscesses were found. In a later investigation an incidence of 0.3 per cent sterile abscesses among approximately 2800 injections was recorded. A similar favourable result may thus be anticipated in this country.

A condition necessary to achieve the full effect of the diphtheria as well as of the tetanus component is, however, that the injections are given at the appropriate times.

Until a few years ago, the general conception was that infants were poor antibody producers. The results of numerous investigations on this subject in past years show, however, unanimously that there is nothing wrong with the mechanism of production per se but that the occasional poor results are due to the presence of passive antitoxin transferred from the mother

TABLE I.

Type of vaccine	Dose of vaccine: 0.02 ml (Di.: 1 unit; Tet.: 0.25 unit; Pert.: 2×10^8 Bc)				Dose of vaccine: 0.002 ml (Di.: 0.1 unit; Tet.: 0.025 unit; Pert. 0.2×10^8 Bc)			
	Antitoxin units per ml serum, geom. mean							
	4 wks after 1st inj.		2 wks after 2nd inj.		4 wks after 1st inj.		2 wks after 2nd inj.	
	Di.	Tet.	Di.	Tet.	Di.	Tet.	Di.	Tet.
Di-Tet-Pert. + $Al(OH)_3$	0.18	0.15	13.0	14.4	< 0.0013	0.00007	0.093	0.41
Di-Tet-Pert. − $Al(OH)_3$	< 0.0011	0.0051	0.23	6.55	< 0.001	0.000022	< 0.001	0.00058
Di-Tet. + $Al(OH)_3$	0.019	0.024	9.31	18.1	< 0.001	0.00004	0.011	0.018
Di-Tet. − $Al(OH)_3$	< 0.001	0.0026	0.0016	0.42	< 0.001	0.00004	< 0.001	0.00008

via the placenta, which by neutralizing the specific antigen in the vaccine inhibit or even entirely prevent active immunization.

Quite simple quantitiative conditions appear to cause the inference, and Glenny, Barr and co-workers in particular have elucidated these conditions in England as regards diphtheria vaccine by means of very extensive investigations in children. If the child has a titre of passive antitoxin of over 0.04 antibody units per ml when the active immunization is commenced, this leads to significantly lower average values than in children who have lesser quantities of passive antitoxin.

Passive homologous antitoxin is excreted at the rate of approximately 15 per cent per week. As the infant is born with approximately the same titre as the mother, the earliest point for commencement of vaccination against diptheria can be calculated if fairly reliable information is available regarding the diphtheria antitoxin level in the population.

An analysis of the routine measurements of diphtheria antitoxin, just completed, in 50 convalescent and normal human serum mixtures representing 5–700 adults showed that 26 per cent of these mixtures contained over 3 antitoxin units and 64 per cent about 0.5 units on an average (arithmetical).

From the standpoint of diphtheria prophylaxis, this is a very comforting

result, but in this particular connection it complicates the situation since it implies that about $\frac{1}{3}$ or more of infants in Denmark at present are born with 1 unit of diphtheria antitoxin per ml or more. With a loss of 15 per cent per week, these children will not reach a concentration of antitoxin at which a satisfactory result may be anticipated from diphtheria vaccination until the age of about 4–5 months. In a few years, when the generations since the introduction of the combined diphtheria-tetanus vaccine in 1950 have grown up, the same will hold true for tetanus vaccination.

It is presumed that, seen against this background, it will be agreed that the time for diphtheria-tetanus vaccination which is, at present, about the 5th month, should not be advanced. It then becomes debatable if the object of introducing triple vaccine, viz. to reduce the number of injections, is, in fact, achieved. This depends on the age when vaccination against whooping cough ought to take place. If immunity to whooping cough is considered imperative prior to the age of 4–5 months, and if the first health examination is utilized for the first injection, the 3 first injections of whooping cough vaccine will be administered at the ages of $1\frac{1}{2}$, $2\frac{1}{2}$ and $3\frac{1}{2}$ months. To employ triple vaccine in such small infants is more or less a waste of the diphtheria and tetanus components and is, therefore, to be condemned on economic grounds alone. At the age of 5–6 months, at the time of the 2nd health examination, vaccination against diphtheria and tetanus should be undertaken and if triple vaccine is employed for this, the whooping cough component will probably be superfluous for all children who were vaccinated against whooping cough in early infancy. Where the final diphtheria-tetanus vaccination one year later is concerned, triple vaccine would reduce the number of injections, provided that a booster dose of whooping cough vaccine is considered necessary.

The situation changes if the immunization for whooping cough can be postponed for some months. By commencing triple vaccination at about the 5th month and administering the 2 other injections at the ages of 6 and 7 months, 2 injections are avoided, but whooping cough immunity cannot then be anticipated until the age of 8 months.

The author is of the opinion that the choice between these 2 possibilities must decide whether triple vaccine can be employed to advantage in Denmark.

Programme of Immunization

Sv. Tulinius, Departmental Chief at the State Serum Institute: A programme of immunization must be planned in view of the epidemiological situation, the modes of prophylaxis available and the programme of immunization already in action.

No direct parallel can be drawn with other countries which have other epidemiological conditions and another historical development of active immunization. Both the attitude to a certain immunization and the particular immunological conditions must be taken into consideration.

An account was given for the incidence of whooping cough in the two 5-year periods from 1946–1955 and it was hereby shown that 10 per cent of all the cases occur in the age group 0–1 year. It was shown, further, that 75 per cent of all the deaths occurred during the first year of life and more than half of these deaths in the first 6 months of life. It was stressed that whooping cough plays a significant role both in the bodily and mental development, particularly in very early infancy. The social aspect of the inconveniences both in the home and in institutions for children was mentioned.

A series of investigations regarding the efficacy of vaccination against whooping cough were mentioned, e.g. that in England, employing good vaccines, the number of cases of whooping cough was reduced from 87 per cent to 14 per cent among children who had been exposed to massive infection with whooping cough in the home. Laboratory standardization of the vaccine was similarly rendered possible by the extensive field investigations. It appeared that 3 injections at intervals of approximately 4 weeks were necessary to achieve reasonable protection and protection for at least 2 years could be anticipated. Various examples of immunization practice in different countries were mentioned.

The question of early immunization during the first months of life with pure whooping cough vaccine as opposed to somewhat later immunization from about the fifth to sixth months of life was considered in more detail, and it was demonstrated that not so many injections were avoided as might be anticpitated by postponing whooping cough vaccination until the time for diphtheria-tetanus vaccination. It was further pointed out that the number of complications is considerably greater when combined vaccines are employed and that a combined whooping cough-diphtheria-tetanus vaccination cannot routinely be carried out in the same way and to the same extent as pure diphtheria-tetanus vaccination on account of the risk of cerebral complications.

Two alternatives are suggested: early immunization with pure whooping cough vaccine commencing with the health examination at the age of 5 weeks and continued in the 9th and 13th weeks of life. In this manner, considerable reduction in the morbidity and mortality in the first 6 months of life can be anticipated. Contrasted with this is the later immunization with triple vaccine by which immunization is certainly simplified but the object of protecting children at a period of their lives when they are particularly exposed is not achieved.

Finally, the author did not recommend a programme of immunization in which triple vaccine, double vaccine and pure whooping cough vaccine are employed as this must be considered to involve far too many difficulties.

Discussion

It had been hoped in paediatric circles that the mixed vaccine for diphtheria and tetanus now employed could be united with vaccine for whooping cough so that all children could be vaccinated with such a triple vaccine as early as possible. The impression is prevalent that in other countries favourable experience has been gained with such vaccination so that it should also be employed in Denmark. After the information given in the introductory lectures, it was debated whether the early pure whooping cough vaccination and the slightly later vaccination against diphtheria and tetanus should be preferred, or if triple vaccine should be employed at the slightly later period.

P. Plum suggested that as a commencement, at any rate, the latter method should be employed. Professor Plum was supported in this by *P. Drucker* and *C. Friderichsen* who emphasized that children should not be submitted to more injections than necessary and therefore proposed triple vaccination at the ages of 4, 5 and 6 months. *F. Neukirch* stressed the fact that the disease was particularly serious in infancy and recommended vaccination for whooping cough as early as possibly. *J. Ørskov* emphasized that early pure vaccination against whooping cough is immunologically the most correct procedure. *K. Bojlén* stressed the increased risk which abscess formation and other reactions imply to spoil the now well established reputation of diphtheria-tetanus vaccination. *F. Bruhn-Petersen* reported from general practice that he and his partner commenced general prophylactic vaccination against whooping cough 6 months ago. The vaccine was offered to all children brought for health examination at the age of 5 weeks and was administered 3 times at intervals of one month. All the mothers accepted the offer. No complications occurred and no case of whooping cough occurred among the vaccinated infants although many of them had siblings with whooping cough.

After further discussion of the problems, paediatricians were most in favour of discarding early whooping cough vaccination and recommended triple-vaccine from the age of 5 months as a general rule. The individual practititioner should, however, be free to choose the mode of vaccination. In view of the risk of complications it was proposed that triple vaccine be administered, until further notice, to a limited and easily controlled clientele,

e.g. children in institutions. Triple vaccine is not yet available and production can commence in about 6 months at the earliest.

The discussion closed with a request from the Danish Paediatric Society to the National Serum Institute to commence production of triple vaccine for prophylactic use. When this is available, vaccination will be instituted under the auspices of the Danish Paediatric Society and in co-operation with the National Serum Institute of a limited material of children at the ages of 5, 6, 7 and 18 months.

The National Serum Institute consented to co-operate in such an experimental scheme.

Acta Pædiatrica 47: 628—639. Nov. 1957.

The Danish Paediatric Society

Meeting, December 5, 1956

J. Vesterdal: **Arthrogryposis multiplex congenita.**

In the case demonstrated, the knees and elbows had stiffened in the extended position and there was extreme palmar flexion of the hands. In addition, an extreme degree of bilateral clubfoot and dislocation of the left hip were present. No similar cases in the family. In the fifth month of pregnancy the mother fell with her scooter but did not, however, sustain any injury to the abdomen. The pregnancy was otherwise uneventful.

Discussion.—*E. Thamdrup* has seen four severe cases of arthrogryposis in the course of two or three years. The etiology is probably not identical in all cases. The combination with other congenital deformities suggests that some factor influencing embryological development may be present. In two cases the author demonstrated histological changes in the connective tissue of the skin by biopsy similar to those in cutis hyperelastica (Ehlers–Danlos syndrome). Cases have also been described previously of combined arthrogryposis and Ehlers–Danlos syndrome. It appears, therefore, that in some cases at any rate more generalized disorder of the mesenchymal tissue is present such as may also be the case in osteogenesis imperfecta which has been observed combined with Ehlers–Danlos syndrome (Biering and Iversen, *Acta pædiat.*, *44*: 279, 1955 and *45*: 656, 1956). Generalized cortisone therapy in one patient with arthrogryposis and intra-articular hydrocortisone injections in another were unsuccessful.—*Sv. Brandt:* Patients with this disease are not uncommon in orthopaedic departments. He agrees with Dr. Thamdrup that spinal changes are frequently absent. —*P. Plum* seeks information concerning the treatment employed in orthopaedic departments and the results obtained and proposes consideration of appropriate cooperation between the paediatric and orthopaedic departments as regards treatment.—*Rasmussen* is about to analyse the results at the Orthopaedic Hospital, Copenhagen.—*R. Wichmann* quotes one case in which a certain result was achieved.—*Henn. Andersen* asks whether treatment of the tense soft tissues with hyaluronidase has been attempted.—*Englesson* has attempted such treatment but without effect. He stresses that feeding presents difficult problems and for this reason transferrence to an orthopaedic department must frequently be postponed.

J. Vesterdal: **Collection of urine in infants by means of "coloplast" plastic colostomy bag (Demonstration).**

Knud Aagaard **and** ***Henning Letman:*** **Thalassaemia occurring in a Danish boy.**

The boy suffers from congenital hypochromic anaemia of haemolytic type and refractory to iron. Splenectomy undertaken at the age of 5½ years did not alter his condition

and the haemolytic character of the anaemia beame even more pronounced. At the age of 8 years the Hb % is 55 (8.1 g %), mean haemoglobin concentration 31 g %, mean corpuscular volume 81 μ^3. Out of the 3.20 mill. erythrocytes per mm^3, 0.7 % are erythroblasts and 28 % reticulocytes. The erythrocytes are thin with greatly increased osmotic resistance and a slight tendency to rouleau formation; in smears, target cells predominate; they contain 56 % foetal haemoglobin. Leucocyte count 14,000 per mm^3, normal forms. Thrombocyte count 360,000 per mm^3. The bone marrow is very cellular (81 % erythroblasts) and corresponding to this slight radiological bone changes are present. The parents are first cousins and neither suffers from anaemia but in both the erythrocytes have a slightly increased osmotic resistance and contain 2.5 % and 3.5 % foetal haemoglobin, respectively. The clinical picture in the boy cannot at present be differentiated from that of thalassaemia major despite the fact that all 6 great-grandparents were born in Denmark.

Torben Iversen: **Reticuloendotheliosis.**

The clinical picture of a case in a boy aged 18 months is described. This comprized anaemia, hepato-splenomegaly and generalized enlargement of the lymph glands. The disease developed at the age of 14 months and has remained more or less stationary. Haemoglobin approximately 70 %; blood sedimentation rate approximately 20 mm; leucocytes 15,000–20,000; monocytes 25–30 %; thrombocytes approximately 150,000; gamma globulin 1.54–1.84 g %. The bone marrow does not show any definite sign of leukaemia and the spleen, liver and lymph glands show proliferation of the reticulum cells. Diagnosis:? atypical Letterer-Siwe's disease,? monocytic leukaemia in the pre-leukaemic phase.

Torben Iversen: **Congenital hypoplastic anaemia.**

The congenital anaemia, congenital pancytopenia (Fanconi) and congenital hypoplastic anaemia (Diamond, Blackfan, Josephs) are mentioned. A case of the latter type occurring in a boy aged 12 months is reported. Increased amino acid excretion was demonstrated. Treatment with cortisone and ACTH was without effect. The patient requires regular blood transfusions.

J. Vesterdal: **Familial goitre, myxoedema and partial deafness in two sisters.**

Two girls were demonstrated both of whom were very small but well-proportioned. The elder, aged 11 years, was 3 feet 11½ inches high (121.5 cm, or 21 cm less than average) and had a bone center development corresponding to 8 years. The younger, aged 8½ years, was 3 feet 6½ inches high (109.5 cm, or 20.5 cm less than average) and had a bone center development corresponding to 6 years. Both had goitre and in both the protein-bound iodine in the serum is 1.1 μg per cent. Both had greatly impaired hearing and otological investigation revealed acustic neurolabyrinthopathy. According to the mother, both could hear until the age of one year after which the hearing deteriorated. These sisters have a healthy brother and a healthy sister but the following members of the family have reduced hearing and goitre: both parents, the father's sister, both the maternal grandparents and two siblings of the maternal grandfather.

H. Dyggve: **A case of Turner's syndrome (Demonstration).**

Harald Gormsen: **Sudden, unexpected death in infancy.**

An account is given of the 431 legal autopsies on infants (0–2 years) undertaken during the years 1945–1956 inclusive in the University Institute of Forensic Medicine, Copenhagen. The police in Copenhagen request legal autopsy of all infants found dead and in practically all cases of unexpected death in this age group. Dr. Tyge Jacobsen and Dr. Jørgen Voigt have analyzed the material from the Institute from the 10-year period 1945–1954 (a total of 356 cases, published in *Acta medicinae legalis et socialis, 9*: 117, 1956). Out of these 356 cases, 259 (i.e. 73 %) were of "natural" death in infancy, the remainder consisted of perinatal death (50), infanticide (18) and accidents (29). Sixty-five per cent died in the first 6 months of life, 25 per cent in the second 6 months and 10 per cent between 1 and 2 years of age. On the basis of the autopsy findings and supplementary investigations, the cause of death was satisfactorily elucidated in 25.5 per cent of cases; the cause of death was relatively well elucidated in 37.1 per cent while the cause of death had to be termed obscure in 37.4 per cent (histological and bacteriological investigation not carried out systematically). In 117 cases (i.e. 45 %) infection was demonstrated as the cause of death and of these acute respiratory infection in 91 cases. Aspiration (as the only finding) was found in 16 cases. Congenital heart disease was the cause of death in 10 cases. In 50 consecutive cases of sudden "natural" death in infancy from 1955 and 1956, systematic bacteriological and histological investigations were carried out in connection with the autopsies (published by H. Gormsen & Kirsten Rosendal in *Acta medicinae legalis et socialis, 9*: 161, 1956). The cause of death was presumed to be "external obstruction" in 11 of these cases. In 28 cases there was a history of a preliminary "cold" for a few days and in 9 cases gastrointestinal symptoms had been present. Otitis media was present in 24 cases; in 14 mucopus was found in the rhinopharynx; in 20 mucopus was found in the trachea and bronchi and in 13 in the bronchioli. In 48 acute emphysema was present and in 28 partial; in 8 complete atelectasis and in 12 aspiration of vomit. None of the cases showed macroscopic signs of bronchopneumonia. *Bacteriological* investigation revealed haemolytic streptococci in the tonsils in 6 cases and in 2 of these cases streptococci of the same type were found in the lungs. In 2 further cases, haemolytic streptococci were encountered only in the lungs and the mesenteric lymph nodes, respectively. Non-haemolytic streptococci, staphylococcus aureus, acapsular Pfeiffer's bacillus and pneumococci were frequently found in the tonsils and in the lungs. Pfeiffer's bacillus type b was seen in one case only, in the tonsils, the lungs and in the spinal fluid. Pathogenic intestinal bacteria were not demonstrated in any case, nor were the so-called pathogenic "infant-coli" (26, 55, 86, 111), except as an isolated finding (26), in the spinal fluid of one infant. In none of the cases could it be definitely established that bacteriaemia was the cause of death and the bacteriological examinations afforded no definite guidance. *Virological* investigations (antibodies for influenza A, B and C and APC-virus as well as investigations for Cocksackie virus) were undertaken in a few cases with negative results. *Histological* investigations showed bronchopneumonia in 4 cases, slight interstitial pneumonia in 3 cases and in 32 out of 40 cases examined there were infectious changes in the spleen. On the basis of all examinations performed, the cause of death could be considered fairly well elucidated in 37 out of the 50 cases studied, i.e. in 74 per cent.

Although these "mysterious" deaths in infancy possibly represent a rather complex group, the cause of most of these deaths is undoubtedly acute infection with catarrhal

viruses or other respiratory tract viruses with a fulminant and lethal course on account of special conditions in the infant organism. Further progress in the field of virology will probably unravel the "mystery" surrounding most of these deaths in infancy.

DISCUSSION.—*Oluf Andersen:* With corresponding results as a background, inclusive the low content of gamma-globulin, prophylactic administration of gamma-globulin has been attempted.—*E. Thamdrup* raised the question of a possible constitutional factor. He had recently observed sudden death in 2 siblings.—*H. Gormsen:* Familial cases are not infrequently observed.—*B. Friis-Hansen* stressed the great significance of the social factors: 86 per cent were from poor homes.—*P. Plum* drew attention to the possibility of allergic phenomena and the risk of death from shock. He was less sceptical than the lecturer as regards the diagnostic possibilities and advantages in bacteriological autopsy.—*G. Nielsen* and *P. Bræstrup* stressed the possibilities of poisoning (salicylic acid, codein).—*P. Bræstrup* and *T. Jersild* mentioned that the sudden deaths observed clinically are most frequently due to fulminant laryngo-tracheo-bronchitis.

K. Tolstrup: **A complicated psychosomatic case.**

A boy aged 14 years had suffered from periodic pain in the epigastrium which was relieved by food. He suffered, in addition, from nausea and, to a decreasing extent, vomiting. During repeated examinations in medical and paediatric departments, X-ray pictures were obtained which aroused the suspicion of duodenal ulcer but no definite ulcer changes were observed. A congenital anomaly of the duodenum was also suspected. On account of difficulties at home, which for example manifested themselves as great difficulty in eating, a psychological cause of the abdominal pain was suspected and the boy was observed in the Department of Child Psychiatry, Bispebjerg Hospital, Copenhagen, first for 8 months as an out-patient and thereafter for 6 months as an in-patient. As the abdominal pain persisted, and as neither this nor the anorexia and failure to gain in weight could be explained solely as psychiatric phenomena, renewed X-ray examination was undertaken. A fistula was revealed between the duodenum and the common bile duct but the etiological cause could not be discovered radiologically. On explorative laparotomy a duodenal ulcer was found which had penetrated into the pancreas and with fistula formation into the common bile duct. Following resection of the stomach and establishment of a retro-colic gastroenterostomy, all the somatic complaints disappeared. After a period of observation of 1 year the patient was found to be well. During the first 10 years of his life, the patient had been exposed to severe environmental injury which resulted in severe oral frustration. The boy's psychic structure was characterized by pronounced inhibition of emotions. During his illness this manifested itself by a tendency to suffer in silence and this rendered the establishment of the diagnosis difficult. This was already complicated on account of the singular mode of penetration of the ulcer and the consequently uncharacteristic X-ray pictures. The inhibition of affect was, however, probably also a decisive psychic cause in the development of the ulcer. The psychogenic origin is considered in relation to Alexander's ulcer theory.

It is emphasized that our present knowledge of the pathogenesis of peptic ulceration in children is slight and the psychogenic causes mentioned in paediatric literature have passed relatively unnoticed. The significance of co-operation between paediatricians, surgeons and child psychiatrists in the research concerning this rare conditions is pointed out.

Discussion.—*C. C. Winkel Smith:* The case demonstrates how difficult it may be to establish an organic diagnosis radiologically. It is obvious that laparotomy cannot be considered in the extensive group of children suffering from moderate abdominal pain, but if the attacks are so massive that their intensity is obvious from the appearance of the child or, for example, as a second characteristic, the attacks occur at night when the child wakes with colic and possibly vomiting, this may be an indication for operation. A second difficulty lies in unravelling the mixture of psychic symptoms and organic conditions which not infrequently may occur simultaneously. In the Department of Paediatrics, a child was operated upon on account of suspected Meckel's diverticulum and this was, in fact, found. There was apparently nothing wrong with the rest of the alimentary canal and, accordingly, the psychiatric diagnosis was: probably psychogenic pain. One year later, perforation of the intestine occurred on account of volvulus of the ileum. The way to progress is increased co-operation between psychiatrists, paediatricians and surgeons.—*P. Plum:* May a retrospective analysis of known cases of abdominal colic reveal which errors have been committed?—*K. Tolstrup* doubted this.—*P. Plum:* May the Rorschach test raise suspicion of organic disease?—*K. Tolstrup:* Results of Rorschach tests which are regarded as typical for psychosomatic conditions are known.—*Henning Andersen:* X-ray examination during the attacks of colic sometimes render positive findings.—*Oluf Andersen* stressed that careful taking of the case history not infrequently gives an indication of an organic basis.

Meeting, February 14, 1957

Hans Keiser-Nielsen: **As W.H.O. medical officer in India. A lecture illustrated with lantern slides.**

Meeting, March 13, 1957

Torben Iversen: **Premature puberty in a girl aged 16 months (Demonstration).**

Wulff: **A case of moniliasis (Demonstration).**

Immunization for whooping cough

Discussion, introduced by *Jeppe Ørskov,* Director, and the Departmental Chiefs *Inga Scheibel* and *Svend Tulinius,* the National Serum Institute (Statens Serum Institute). (See this issue of *Acta Pædiatrica* p. 621).

Meeting, April 10, 1957

John Lind: **The closure of the ductus arteriosus at birth.**

Catheterization studies in normal newborn infants (Adams and Lind, 1957) demonstrated the presence of right ventricular and pulmonary hypertension of moderate degree at birth and that the pressure adjustments within the heart following birth take place gradually over a period of several days and not several minutes as was previously supposed. It could further be shown that the ductus arteriosus normally remains functionally patent with a predominantly left to right shunt for several days.

Knowing the pressure relationships in the first 3 days of life it seems quite likely that any procedure which might disturb the infant enough to increase the pulmonary arterial pressure would produce a right to left shunt through the ductus, a fairly common finding in the newborn. The volume of the shunt passing through the ductus will depend on the pressure gradient across it and on its width. The shunted blood recirculates through the lungs and increases the venous return to the left heart and the minute volume of the ventricle. There is thus an increased volume load on the left ventricle. A large shunt acts on the other hand as a hindrance to the delivery from the right ventricle, thus requiring the development of a higher pressure in this chamber (Rodbird *et al.*, 1955). In the newborn the pressure in the pulmonary and systemic circuits are nearly equal and the shunt is relatively small. With the normal unilateral rise in the systemic pressure the left to right shunt increases rapidly and high output cardiac failure may appear.

Ib Boesen: **The diagnosis of patent ductus arteriosus in infants and young children.**

Report of 30 cases with patent ductus arteriosus. The diagnosis was verified at autopsy in 10 cases, at operation in 17 cases, by direct catheterization of the aorta via the ductus in one case and in only 2 cases by angiocardiography. In 17 of the 30 cases the patent ductus was the only malformation or the most important malformation and of these, 11 were less than one year old. Typical continuous murmur was found in 8 cases and 3 of these were in children of less than one year. This murmur was only heard in patients in whom the average pressure in the pulmonary artery was less than half of that in the aorta. Twenty-nine out of the 30 patients underwent cardiac catheterization, by which the ductus could be demonstrated in 21. In 19 of these, the aorta could be directly catheterized via the ductus. In 16 out of the 21 the ductus was the only malformation or the most important malformation. In 2 cases, atrial septal defect with marked left to right shunt was found in addition and in 3 cases coarctation of the aorta. Two of these were of infantile type. These 3 latter complicating malformations were not recognized on catheterization. Twenty-eight out of the 30 patients underwent selective angiocardiography and the ductus could be demonstrated in 23 of them. In 15 of the cases, the patent ductus was the only malformation or the most important malformation and could be recognized by angiocardiography in 14 cases. To sum up, 27 out of 30 cases of patent ductus arteriosus were recognized. In the 3 cases which were not recognized, the patent ductus arteriosus was presumably without decisive significance in the evaluation of the clinical picture (ductus combined with infundibular pulmonary stenosis, defect of the ventricular septum and coarctation of the aorta, respectively). Out of the 17 patients in whom patent ductus arteriosus was the main diagnosis, one died of cardiac decompensation (male, 4 months old). The remaining 16 cases were operated upon and one death occurred in connection with the operation (female, 4 months old).

A. Gammelgaard: **Operation for patent ductus arteriosus in infants.**

Out of 19 cases undergoing operation, 2 were not catheterized; 2 had normal pressure in the pulmonary artery and 9 presented increase of the systolic pressure to between 30 and 60 mm Hg while 6 had a pressure of over 60 mm Hg. Particularly in the age group < 6 months, pulmonary hypertension > 60 mm Hg dominated (75 per cent). It is stressed that experience with the older children showed that the operative risk in closing patent ductus arteriosus was greatly increased when the pulmonary hyperten-

sion was high and that adequate closure demanded resection when the pressure was high. In the group of infants and small children, the operative closure did not present any great difficulty. Ligature was possible in all cases with one exception where resection was required. The closure proved adequate as in 14 of the children who were followed up no murmur could be heard. One death occurred (a child aged 3 months with a pressure in the pulmonary artery of 60/38 mm Hg). The child died 9 hours post-operatively from respiratory failure. Six children suffered from transient post-operative complications taking the form of respiratory difficulties, attacks of cyanosis and poor heart function. The relation of the post-operative complications to the pulmonary vascular changes in connection with increased pressure is mentioned. Measurements of pressure during the operations in 10 children showed a fall in pressure in the pulmonary artery in all cases, but normal values were not obtained when high pressures were concerned. Operation is advised for patent ductus arteriosus in infancy when giving rise to symptoms. The regression of the pulmonary hypertension must be regarded as depending on the early closure of the ductus. The operative conditions favour early operations as the ligature method was adequate and carried a lesser risk. The operative mortality was modest when the high incidence of pulmonary hypertension is considered. In complicated cardiac conditions the ductus was frequently a safety valve for the pulmonary hypertension and its closure implied a risk for right-sided heart failure. The significance of the measurement of pressure during operation to evaluate the possibility of closure of the ductus was discussed.

Fr. Therkelsen: **The possibilities of operative treatment of congenital heart disease in infants.**

An account is given of 76 cases of congenital heart disease in infants in the ages 2–30 months (of these 62 were less than one year old) which were treated operatively. The infants were practically all investigated by cardiac catheterization and angiocardiography in Queen Louise's Hospital for Children. The children were hospitalized partly here and partly in the Paediatric Department, the University Hospital, Copenhagen. Operation was undertaken in Department R, the University Hospital and Dr. Andreassen, Surgeon-in-Charge, has kindly permitted inclusion of a number of cases upon which he operated. The majority of the infants were so ill that they were operated upon on vital indications. In some cases the symptoms were less marked but operation was undertaken as experience has shown that the lesions concerned often lead to death prior to the age of one year (ductus arteriosus with pulmonary hypertension, enlarged heart of other symptoms, coarctation). In a group of 37 cases comprizing typical cases of patent ductus arteriosus with pulmonary hypertension, coarctation of the aorta and the tetralogy of Fallot, the mortality was, approximately, 9 per cent (4 deaths among 37 patients). The remainder of the cases comprize atypical complicated cardiac lesions (trilocular heart + transposition, pulmonary stenosis + tricuspid atresia, etc.) where adequate operation could not be carried out. In two cases, heart-lung machine with Rygg-Kyvsgaard's oxygenator was employed. Twenty-nine out of these 39 patients died in connection with the operation.

I. Rygg: **Experience with lung-heart machine (with film demonstration).**

(No report submitted.)

Discussion.—*B. Friis-Hansen:* How early is the typical machinery murmur heard? —*I. Boesen:* In the 30 children with verified patent ductus arteriosus the murmur was

not heard by us in any infant under the age of 7 months, but cases with typical murmurs have been described already in the first month of life.—*B. Friis-Hansen:* How many infants without murmurs have a patent ductus?—*I. Boesen* was unable to answer this question.—*O. Steinicke:* May a murmur be present in the first months and disappear later but be due to a patent ductus?—*I. Boesen:* Undoubtedly. The significance of murmur in newly-born infants is described in *Acta Pædiatrica, 15*: 2, 169.—*J. Vesterdal:* Is the hypertension in the pulmonary artery which may be observed in older children as a complication of patent ductus arteriosus a persistence of the relatively high pressure in the pulmonary artery in newly born infants?—*I. Boesen:* The problem is unfortunately not elucidated.—*G. Englesson* had heard murmurs develop on the third day. The murmur may thus develop suddenly.—*Oluf Andersen:* Operation should be undertaken as early as possible so that the hypertension does not have a chance of increasing to such an extent that it produces lesions. May persistent ductus arteriosus be classified into 1) hypertension on account of persistent ductus, 2) pulmonary changes which cause increased pressure with subsequent patent ductus?—*I. Boesen:* This problem is not yet elucidated but it is a very decisive problem to solve. Histologists may in future be able to answer the question.—*A. Gammelgaard* and *C. Hansted:* Should all children with murmurs be submitted to cardiac catheterization and angiocardiography?—*I. Boesen:* Only those infants should be submitted to extensive examination who are so ill that operation would be advisable if the investigations reveal an operable lesion.

Meeting, April 24, 1957

K. H. Sparup: **Drug therapy of cerebral palsy.**

Results are presented from the Paediatric Department, the University Hospital (Professor Plum's Out-Patient Clinic for Cerebral Palsy) concerning treatment with Mysoline and the new preparation Miltown (Meprobamat = Restenil = Equanil). In a material of 44 patients suffering from cerebral palsy, 27 of whom had athetosis, definite effect was observed on the hyperkinesia, spasticity and well-being following treatment with Mysoline in doses from 25 mg to 250 mg daily. The effect obtained on the total material was calculated to 68 per cent, and on the athetoid patients alone to 92 per cent. Miltown was employed in 33 patients and an effect on the muscular spasm and the emotional state could be demonstrated in 51 per cent. The preparations were found to possess a certain value as adjuvant preparations in the complex therapy of cerebral palsy.

Sv. Brandt: **Treatment of children suffering from athetoid tetraplegia with Equanil. Report of an investigation with negative result.**

In 12 children between the ages of 1½ and 9 years suffering from severe athetosis, *Equanil* ("Miltown") was compared with a placebo. No difference ascribable to any pharmacological effect could be demonstrated. This negative effect does not exclude the possibility that Equanil may have a sedative effect on adults and older children with cerebral palsy and may thus eliminate the influence of emotional upset causing exaggeration of the incoordinated movements.

Discussion.—*K. Krabbe* drew attention to a preparation named *conein* which became available in the 1920's and proved to be efficacious in spasm of pyramidal origin. The peparation, which was administered in doses of 10 to 80 mg daily, is no longer manufactured but should probably be introduced again.—*P. Plum:* Experience hitherto has resulted in considerable scepticism regarding the effect of drug therapy in cerebral palsy. The impression is gained, however, that mysoline has a certain effect. This impression is confirmed by "old and trained" patients and the testimony of parents. Difficulties regarding the dosage are still experienced.

Hans-Walther Larsen: **Extreme neutropenia occurring in an infant.**

A case of isolated complete absence of neutrophile cells in the peripheral blood and in the bone-marrow of a boy aged 9½ months was reported. The infant had suffered from furunculosis practically continually since birth. The infant had been treated with aureomycin for several periods, The possibility of a toxic effect of aureomycin was discussed. As during cortisone treatment with Meticorten 2.5 mg thrice daily for 8 days, 2.5 mg daily for 2 days and 2.5 mg once daily for 2 days no change in the peripheral blood picture nor increase in the number of extravascular neutrophile cells occurred, the presence of immunological processes was considered to be out of the question. It was concluded that the disease is probably due to a defect in the bone-marrow. The clinical picture is reminiscent of chronic neutropenia but the blood and bone-marrow changes were distinctly more pronounced than those found, as a rule, in chronic neutropenia. The possibility is ventilated that an independant clinical picture is concerned.

Jørgen Kringelbach and *Jørgen Winge:* **Staphylococcal pneumonia in childhood.**

The authors have analysed all cases of pneumonia in the Paediatric Department, the Copenhagen County Hospital, Gentofte, from 1.1.55 until 1.3.57, viz. a total of 228 cases. Of these 6 died. Thirteen cases presented staphylococcal pneumonia or empyema and of these 3 died (23 per cent). Eleven cases were under one year, 7 under 4 months and among these were the 3 which died. A review of these cases of staphylococcal pneumonia shows that 6 of the cases were children from institutions and that in 5 cases staphylococci could be cultured from the lung or pleura and in 4 cases from the naso-pharynx. All cases had infiltrates in the lungs, 9 had pneumatocele, 6 pneumothorax, 3 pyo-pneumothorax, one case had empyema and 6 cases had atelectasis. The leucocyte count varied between 5000 and 32,000 and the 3 patients who died had between 5000 and 10,000. It is concluded that the condition occurs more frequently than previously, and the importance of recognizing the clinical picture is emphasized so that adequate therapy may be instituted immediately.

Discussion.—*J. Vesterdal, Henning Andersen* and *T. Jersild* report some cases of staphylococcal pneumonia from other departments and confirm the impression of the increasing frequency of the disease.—*C. Friderichsen* asks if the pneumatoceles mentioned are not abscesses.—*J. Winge:* The spaces in the lungs which we have described as pneumatoceles are not identical with the expression "chronic lung abscesses". They are of a different etiology and pathological-anatomical picture and are due to distension of the pulmonary tissue on account of the conditions of pressure and subsequent secondary infection so that a fluid level may frequently be seen in them. They are identi-

cal with the spaces which may be found incidentally in children and were for many years regarded as congenital cysts but, following Macklin's experimental work in the 1940's the present conception has been evolved. Concerning *A. Johannessen's* remark that erythromycin might be preferred to terramycin to avoid the risk of staphylococcal enteritis, it should be stated that the terramycin was administered intramuscularly.

P. W. Brœstrup: **Starch dyspepsia in childhood.**

Starch dyspepsia or starch intolerance is the term now usually employed for a condition of dyspepsia which has certain points in common with coeliac disease and which is also encountered in children during dietetic treatment of genuine coeliac disease. There is now such overwhelming evidence to show that the majority, perhaps all, of these cases are due to intolerance to gluten that gluten dyspepsia appears to be a more accurate term. In the course of 2 years, the author observed 25 cases over the age of one year which can be classified in this group and 2–3 of these were borderline cases to genuine coeliac disease. Ten cases were hospitalized and 15 observed as out-patients. Simultaneously, 4 new cases of genuine coeliac disease were treated. Two of these, however, were under the age of one year. The majority of these 25 children had, periodically at least, pale, bulky stools but the main complaints were uncharacteristic symptoms such as abdominal pain, anorexia, fatigue, listlessness and poor, restless sleep. In all cases in which this could be recorded, the growth in length was retarded prior to treatment. On gluten-free diet or only gluten-poor diet all grew normally or more than normally. In the majority this growth was markedly greater than normal. X-ray investigations revealed pathological pictures of the small intestine with irregular dilatations and contractions in the ileum, resembling the picture in coeliac disease. All patients showed considerable clinical improvement on gluten-free diet and in a number of cases when the gluten content was only reduced.

Discussion.—On account of the condensed form of the lecture, a number of the problems concerning details are excluded but some questions about these were answered by *P. Brœstrup,* as follows: To *O. Steinicke:* The diet is not low in fat. The X-ray picture of the intestine is always pathological. The sugar tolerance curve was doubtfully flattened in 8 cases. To *B. Friis-Hansen:* The faeces were not examined for starch grains. To *E. Thamdrup:* The faeces become normal in the course of about a week.—*Gunnar Nielsen* reports that he has treated 3 cases of starch dyspepsia with vitamin D_3. The dose employed was 3300 units daily for a week and was thereafter reduced. From the fourth week the patient received 1150 units daily. No dietary therapy was necessary and good permanent effect was obtained with vitamin D_3 alone.—*P. Brœstrup* has not been able to confirm the effect of this therapy.

Meeting, June 12, 1957

Karen Dreyer **and** ***Svend Nørregaard:*** **Fatal accidents in children.**

The mortality in children from 0–14 years has fallen in Denmark from 647 per 100,000 in 1931–35 to 241 per 100,000 in 1951–55. This fall is mainly due to a reduction in the mortality from infectious diseases and tuberculosis. The mortality in other groups of diseases has only decreased slightly. This holds true for tumours and accidents. At

present, between $\frac{1}{2}$ and $\frac{1}{3}$ of all deaths occurring among children are due to accidents as compared with approximately $\frac{1}{10}$ at the turn of the century. The total mortality attributable to accidents in children from 0 till 14 years in Denmark has remained practically unchanged from 1931–35 to 1951–55. Behind this apparently unchanged mortality, however, a decreasing mortality for certain categories of accidents and an increasing mortality where other categories are concerned are camouflaged. The mortality from accidents due to motor vehicles has, in particular, increased violently, especially in boys and this category shows a very high absolute figure. Other traffic accidents do not have such great significance. Drowning accidents are of great significance and in small boys the number increased steadily until approximately 5 years ago. Suffocation is the most important cause of death in infants. In this category, too, a steady increase in the incidence has been observed with the exception of the last 5 years. Mortality from falls has, similarly, the greatest significance in small children. The number of fatal burns has shown a very significant fall during the period mentioned, particularly where the smallest children are concerned, but it is still of great significance in infants. Poisoning has only a slight numerical significance. In discussing the possibilities for prevention of accidents in children, special attention was paid to the "accident-prone". As accidents in the home still comprise a great proportion of the accidents, it would not be correct to base the prophylaxis solely on the traffic accidents. (To be published in the *Danish Medical Bulletin.*)

Discussion.—*B. Friis-Hansen:* Among the traffic accidents, how many of the children were passengers in the motor vehicles and how many were pedestrians?—*Sv. Nørregaard:* Only a minority were passengers.—*E. Thamdrup:* Why is suffocation more common in boys than in girls?—*Sv. Nørregaard* was unable to answer this question.—*P. Bræstrup* enquired about the number of drowning accidents in garden ponds. —*Sv. Nørregaard:* 1945–50: 30 deaths, 1951–55: 15 deaths.—*Annalise Dupont* enquired about the relation between intelligence and accidents.—*Sv. Nørregaard:* As with all other handicapped children so also with the mentally sub-normal: the moderately affected children have a higher incidence of accidents than the average while the severely affected cases show a lower incidence than the average, probably because the latter live in a more protected environment.

***Harald Kreutzfeldt* and *Ellen Johansen* (Health Visitor): Attendance at health examinations of children.**

The object of the investigation was to check the attendance at the free, regular health examinations available in Denmark of children from birth onwards at a definite occasion, viz. at the age of 15 months. It was found that only 50 per cent of the children at this age had attended such an examination by the general practitioner or a child-welfare institute. In 15 per cent the mothers stated as the cause of the defaulting that the child was in a day nursery and the mothers considered that the regular medical examinations there were sufficient. In 29 per cent the cause stated was that the child was ill or that the mother was ill or in some way prevented from attending about the time when the examination should have been performed. Only a few mothers had criticism to make and the majority gave the reason that they had forgotten the examination. Practically all the mothers wished to continue the health examinations of the children and yet only half of them attended within 1–2 months for the neglected examination. It is concluded that if better attendance at health examinations after

the first year of life is desired, the most important measure would be to extend the checking by the health visitors, which ceases after the first year, to a longer period.

Discussion.—The question was discussed whether attempts should be made to maintain the attendance of as many children as possible and the possibilities for this, or whether efforts should be concentrated on the groups which particularly require control. *Heinild* suggested that a social worker should be available at the examinations.

Pediatric Society of South Sweden

Meeting, March 31, 1957

Nils Lindquist: **Familial dysostosis.**

A boy, who was the only and elder sibling of a typical case of gargoylism, exhibited from birth certain retardations in development: he weighed at 1 year of age only 7700 g, had pronounced lordosis, a large head, remarkably short legs and a relatively long trunk, was manifestly bowlegged and had coarse and broad hands and feet. At 1½ years of age he resembled a case of "partial chondrodystrophy". The psychical development was completely normal. At 7 years of age he was 102 cm tall, had a moderate spinal curvature, short thighs and somewhat defective extension of both elbow joints. The femoral diaphyses and tibial epiphyses exhibited irregular attenuations, surrounded by a slight sclerosis (Fig. 1). The roentgenologic skeletal age corresponded to the patient's age. The basal metabolism on two occasions was + 23 % and + 33 %. The cholesterol value was 270/mg. The patient is now 12 years old, 124 cm tall (normal range of variation = 130–166 cm) and weighs 32 kg. He is strongly built with a strikingly well-developed musculature. The head circumference is 56.3 cm. The lower extremities are rather short, the sitting height is 59 % of the standing height (normally 53–55 %). The hands and feet are rather short and broad. The corneae are normal. He still exhibits the same changes in the femoral and tibial epiphyses. He does well in school, is lively and happy. The growth disturbances in the two brothers probably have a common background, even if the elder brother lacks the characteristic symptoms of gargoylism. The elevated cholesterol value is of interest in connection with Cocchi's findings of increased cholesterol values strikingly often in gargoylism in comparison with other dysostoses and the fact that forms of gargoylism have been reported with typical symptoms first after 20 years of age. In several quarters cases of gargoylism and Morquio's disease have been observed among siblings. This boy shows no clinical symptoms similar to Morquio's disease. The boy can be designated at present as an endochondral dysostotic, whose development has been very similar to that in chondrodystrophy. There is clearly an obvious relation between gargoylism and Morquio's disease. There is also a close familial connection, as has been shown here, between gargoylism and a growth disturbance with a clinical picture which is quite unlike that of either gargoylism or Morquio's disease. It can therefore be questioned whether the syndromes designated as gargoylism and Morquio's disease can be extreme variants of the same fundamental disease whose real cause is obscure and of which this boy represents another symptomatic variation.

J. Larsson: **Clinical symptoms of Meckel's diverticulum.**

Meckel's diverticulum is the most common anomaly in the digestive tract. Boys are afflicted more than twice as often as girls. More than half of the cases with pathologic symptoms exhibit these symptoms during the first 3 years of life. There are great variations regarding the form, size and location. The gravest complication is ileus, usually strangulation ileus. On such an occasion circulatory disturbances develop rapidly. In intussusception due to Meckel's diverticulum the average age is about 5 years, whereas in other cases of intussusception it is around 2 years. The most interesting complication is peptic ulcer, half of which usually become perforated. Melena is the most constant Meckel symptom. Ulcer is most common in small children, obstruction in older ones. Meckel's diverticulum should be removed, preferably when it is detected, because of the great risk of dangerous complications.

L. Essen-Möller and *S. Lundholm:* **Retrolental fibroplasia at the Banck Hospital.**

The series of cases comprises 200 immature infants treated at the Banck Hospital in Hälsingborg from 1952 to 1956. Only cases with positively demonstrated retinal detachment in some part of the periphery of the fundus or certain pathological ramifications of the vessels have been diagnosed as fibroplasia (fpl.). Twenty-six such cases, or 13 ‰, were found in the material: in the weight class 1000–1495 g, 7 of 10; in 1500–1995 g, 17 of 49; in 2000–2495 g, 2 of 141. Among the 61 infants who had received oxygen 24 fpl. were found. In the second of the mentioned weight classes there were 17 fpl. of 34 oxygen-treated infants, but no fpl. among 15 who had not received oxygen. Two infants who had not received extra oxygen exhibited fpl. One of these was a slight case with a birth weight of 2200 g and the other somewhat more advanced with a birth weight of 1440 g. Both healed without any visible residues. In at least 2 cases fpl. occurred while the infant was in an incubator. Fpl. was on the average more severe in girls than in boys, but the average birth weight of the girls was lower. Of the 26 fpl. cases in the series there were no less than 12 twins. The fpl. frequency among the twins in the material was 12 of 50, among the other infants 14 of 150. In the group 1500–1995 g there were 10 fpl. of 17 twins and 7 fpl. of 32 of the other infants. Most of the children have been re-examined. Two infants became totally blind. At the last examination the fpl. had regressed completely or with clinically insignificant peripheral changes of a mild sort in 24 of 27 cases (for this comparison 2 cases from 1951 have also been available). The healing tendency in the cases is thus surprisingly high. These cases never would have been diagnosed if systematic examinations had not been made. Some of these 24 cases had had very severe and extensive retinal detachments and gross circulatory changes. Some cases of myopia have already been ascertained.

Folke Hedenberg: **Anicteric hepatitis in an infant with unusual symptoms.**

A 2¼-month-old girl had previously been in good health with a good appetite and a normal increase in weight. One week before admittance she began to eat less, became fretful and high-strung and had a big abdomen. She was admitted with nose bleeding, and petechiae in the skin and the oral mucous membranes. The prothrombin index lay constantly between 12 and 17, unaffected by large doses of vitamin K. No visible icterus. Meulengracht 1:14. Thymol 0.28. Thrombocytes 71,000–84,000. Examination of the different clotting factors showed a pronounced decrease in prothrombin, proconvertin

Fig. 1.

and proaccelerin, moderate decrease in fibrinogen. Total albumin 4.5 % and 4.7 %. ESR constantly low, 3 mm. Constant galactosuria. Marked increase in the amino acid excretion with exception of the high-molecular neutral acids. Increase in non-protein nitrogen, ketonuria and development of ascites. Remarkable absence of jaundice. The girl was treated with deltacortone and blood transfusions without effect. She died 1 month after admittance. *Autopsy findings:* The liver was large and pale with pea-sized, yellowish green, compact granulations on the surface as well as on the section. Microscopic examination revealed subacute-subchronic hepatitis with sparse adenomatous parenchymal regeneration. The spleen, pancreas and kidneys were essentially normal. The *etiology* of this anicteric hepatitis is obscure. Galactosemia was predominant, but cataract and albuminuria, regarded as obligatory findings in this disease, were lacking. There were no indications of viral hepatitis. It has been propounded that the anicteric form of viral hepatitis more than the icteric develops into progressive liver disease. Craig *et al.* have distinguished as a special group "cirrhosis without previous predisposing disease", where the etiology was most often obscure. There is an agreement between the case described here and several of their cases both clinically and pathologico-anatomically.

Transactions of the Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, May 29, 1957

Å. Gyllenswärd: **Fits of unusual origin.**

A seven-year-old Lappish girl from a nomadic family has for 2 years suffered from fits of unconsciousness and minor convulsions with increasing frequency. They appear to be provoked by fright, exertion and perhaps also hunger. She is number 6 of 7 siblings. One brother died at the age of 5 years in convulsions of unknown origin. Two uncles died of unknown cause at an early age, and they probably did not have convulsions. Physical and neurological examinations, the usual blood and urine investigations, blood chemistry, EEG and X-ray of heart and lungs gave normal results. ECG in resting state revealed a Q-T interval at the upper limit of normal. Ergometric test of the working capacity resulted after only two minutes of easy exertion in an ectopic heart activity with a high frequency of different types of ventricular extrasystoles. At that time there was no sinus-rhythm at all. As the exertion was continued the rhythm became progressively regularized in 5 minutes and the heart rate decreased from 200 to 140. The respiration was maximum 75 per minute and decreased during the continued exertion to 55. It is supposed that this girl has a familial disease, perhaps a metabolic anomaly in the heart muscle.

Discussion.—*Tage Möller:* Report of a case, a 3-year-old deaf-and-mute boy, presenting an almost duplicate clinical picture with attacks of unconsciousness and cramps. This condition is by and large elicited by physical and psychic exertion. Attacks are readily provoked by being frightened, as for example by needle-punctures for blood tests. ECG showed prolonged QT time together with certain changes indicating myocardiac damage. Like Gyllenwärd's case, arhythmias of extrasystolic type occurred during attacks. EEG during attacks showed signs of hypoxemia. Otherwise normal conditions. We considered this a case of coronary circulation anomaly in which the left coronary artery arose from the pulmonary artery. A few days ago I received a letter from the child's mother in which she stated that the boy was still alive, but that he was much troubled by recurrence of the above-mentioned severe attacks which occasionally seemed threateningly fatal. During attacks he was administered oxygen according to our directions and this seemed to exert a beneficial effect and occasionally even a prophylactic action in preventing attacks. We have not dared to attempt any cardiac catheterization or angiocardiography on this excessively fragile and sensitive child.

H. Ekelund: **Lead poisoning.**

Report of two cases of lead poisoning, where the source of poisoning was at first obscure and a very detailed penetration of history was necessary. *Case 1.*—Boy 3 months old. Four days before admission increasing and frequent vomiting, was not able to keep down any food except tea. On admission rather healthy-looking though pale. Continued vomiting. No diarrhoea. Some type of intoxication was suspected. Thorough investigation of history revealed use of bath-thermometer with freely exposed

lead lump (to keep thermometer vertical in bath). Mother used the thermometer while cooking the boy's formula. Analysis of milk sample showed abnormal lead content. History, hematological findings and finally roentgenological evidence of lead lines confirmed the diagnosis. *Case 2.*—Boy 3½ years old. Three months before first admission tired, apathetic, vomiting, "everything was foul-smelling". On admission clinical, hematological and roentgenological evidences of lead poisoning. Treated with EDTA with good result. No source of poisoning detected in spite of extensive investigations. One month's stay in the clinic. At home for two weeks but getting worse already after a couple of days. Admitted here again. *Diagnosis:* Lead poisoning. Evidence of having ingested more lead at home. A second successful treatment with EDTA. Two months stay in the clinic. Intense search for lead source, which was located at last in orange juice, made by his mother out of oranges, sugar and what was thought to be a powder of citric acid, but eventually turned out to be a lead salt.

S. Edlund: **Hypertension in unilateral kidney disease.**

An 8½-year-old girl with hypertension of 190/145–160/120. History of pyelitis at 6 months and 1½ years. ECG and X-ray of heart within normal limits. Fundus oculi changes in calibre of vessels and narrow arteries. Blood chemistry normal. Urinary investigations show a maximal concentrating power to 1.014. Daily urine volume 800–1500 ml. Normal excretion of noradrenalin and enteramin. Clearance tests show slight lowering of PAH and blood flow. Urography: left kidney shrunken. Aortography: left kidney shrunken and pre- and paraaortic regions apparently occupied by a tumour which was provisionally diagnosed as paraganglioma. On exploration this was found to be chronic adenitis resulting from pyelonephritic left kidney, which was removed. Postoperative lowering of blood pressure to 120/80, and rise in specific gravity to 1016 (without restriction of fluids).

R. Debré: **Cat scratch disease.**

Several years ago we recognized, in conformity with Lee Foshay of Cincinnati, this disease entity and already in January 1950 we described it in collaboration with Maurice Lamy and others under the term "Cat scratch fever" (Maladie des griffes de chat). Subsequently in many countries (Europe, Asia, Africa and America) more than 700 observations have been published. Personally we have studied more than 100 cases. The contact with cats, according to statistics, varies from 83 % to 98 % and traces of cat scratches are found in about 60 % of the cases. The involved cats are always healthy. Family epidemics have been observed and also a village epidemic (9 cases). The clinical picture is characterized by an inconstant inoculation lesion (50 %) formed as a papule and afterwards as vesiculous pustule. A cold abscess is always observed, slightly painful, which suppurates in every other case and produces a fistule which heals spontaneously without leaving a scar. Fever may be absent or marked. Fatigue is more or less pronounced. In certain instances one observes tonsillitis with cervical adenitis. One has denied the occurrence of thoracic and mesenteric adenitis. One unique complication should be mentioned besides erythema nodosum and certain eruptions, viz., the nervous localization, essentially a curable encephalo-meningitis (12 such observations are reported by W. B. Daniels and F. G. MacMurray as well as by myself with S. Thieffry and others). Diagnosis is established by the intradermal reaction with

antigens consisting of diluted and tyndallized lymphonodular pus. The reaction is specific inasmuch as the 41 cases found to be positive among healthy individuals all occurred among veterinarians and persons having had repeated contacts with cats. The lesion is characterized by a ganglionary granuloma which suppurates after becoming necrotic. The etiological virus is unknown. Treatment is irrelevant and cortisone may shorten the duration of a spontaneous cure.

Discussion.—*A. Wallgren:* One reason that no case of Cat scratch fever has as yet been reported in Sweden may be that our country has far fewer cats than most southern countries. Since most of the country's pediatricians are familiarized with the clinical picture of this disease, I believe that they will bear it in mind when confronted with suspicious cases. May I ask if it is possible to obtain intradermal test material and, if it is possible, from where?

R. Debré: It can be obtained from the Bacteriological Laboratory at l'Hôpital des Enfants Malades in Paris.

***R. Lightwood:* Home-care for sick children.**

For technical and scientific reasons much of the work formerly handled in our western communities by general practitioners has, in recent years, been transferred to the hospitals (social factors sometimes operating in the same direction). We have to face the fact that there has been an encroachment on the sphere of responsibility of family practice which will not, in the long run, be for the good of the community. With the expansion of the hospital services the skill and responsibilities of hospital physicians has greatly increased but the technical quality of general practice has not kept pace; thus, while the status of hospital practice has risen in the eyes of the public, that of ordinary family practice has declined. In England this change in the relative importance of the two branches of practice has been influenced by the introduction, in 1948, of the National Health Service in which every family is entitled to the services of a family practitioner, but the hospital service has been greatly expanded and the public are turning more and more to the hospitals. It is even happening that many patients are being treated in hospital when a competent family doctor with the necessary resources could do the work just as well at home. Moreover, the cost of hospital care is very high, and there are several other disadvantages in using it too much, especially in the case of young children. Paediatricians have the duty of watching the interests of children and seeing that the hospitals are correctly used. With falling birth rates, improved child health and decreasing morbidity, less recourse to hospital might be expected, but there is little sign of this as yet. At St Mary's Hospital in London, before our home-care project started in 1954, we estimated (Lightwood, 1956) that one-quarter of the children in hospital, during a review period, could have been managed at home if the doctors had possessed the necessary facilities and training. Clinical teaching must be properly related to the real needs of the patient and even the apparent need to keep beds occupied for the teaching of students and nurses should not encourage unnecessary hospital treatment.

A project for the home-care of sick children was started at St Mary's Hospital in 1954 and this project has dealt with nearly one thousand cases in just over three years. We have arranged that this home-care project is centred in our hospital, but that the patients we help to treat, remain in the care of their family doctors whom it is our aim to support by supplying technical help and the mobile diagnostic and therapeutic resour-

ces of the hospital. The aims of the project are: (1) to improve the liaison between the family doctor and the hospital, (2) to save unhappiness and unnecessary emotional disturbance, as well as to prevent cross-infection in hospital, (3) to cut the cost of treatment *while maintaining the highest standards of care.*

The plan depends on a small mobile team of fully trained paediatric doctors and nurses who give technical assistance to the family doctor on request. In this way all the ordinary diagnostic and therapeutic procedures, customarily performed in hospital, can be carried out at home. Although a home-care project organized on these lines is more valuable in a city than in a more sparsely populated area the advantages are considerable. In addition to saving admissions, and sparing beds for surgical and accident cases, the plan has established excellent working relationships with the general practitioners; many of the mothers have benefitted from the experience of helping in the restoration of their child's health, and not least, the hospital staff, medical and nursing, have had valuable experience not obtainable in hospital which can be used in teaching.

Reference may be had to: Lightwood, R. (1956), The home care of sick children. *Practitioner, 177,* 10; Lightwood, R. *et al.* (1957), A London trial of home care for sick children. *Lancet, I.*

Discussion.—*A. Wallgren:* I would like to ask Dr. Lightwood how one proceeds when the patient's mother engages in outside work and the child is placed in a day nursing home and there contracts an upper respiratory infection? Is the child than admitted to a hospital or is its mother compelled to take care of the child at home? I should also like to know if the home-care system is made use of in teaching medical students, which apparently would seem of paramount value to them.

Bengt Hagberg: **Abdominal migraine in children.**

Three cases with violent recurring abdominal pains of cerebral origin were reported. Two of them closely simulated intussusception. The third concerned a girl 13 years of age with very severe attacks of more continuous periumbilical pain, marked pallor and stickiness. Intravenous choleography was repeatedly pathological (no contrast filling) during attacks, but quite normal during free intervals. Like the other two cases this girl had an abnormal EEG. The pathological findings in her case were most pronounced over the right temporal region. All three cases responded only to anti-epileptic treatment. Recurrent abdominal pain of cerebral origin is a clinical reality of practical and theoretical interest. It is probably not too uncommon. Some of the cases are more related to migraine and its equivalents in their clinical picture, others to epilepsy. The borderline between these two otherwise divided diseases seems to be especially difficult to draw when visceral symptoms dominate. The electroencephalographic findings and the benefit from anti-epileptic treatment are some of the things arguing for an epileptic origin. For psychological reasons, however, it seems to be better to call the syndrome abdominal migraine rather than abdominal epilepsy at least when no other epileptic symptoms are present.

Discussion.—*M. d'Avignon* describes 2 cases of recurrent severe abdominal pains in children. In both cases the EEG changes consisted of slow high amplitudinous activity with quick potential alternations of the spiked type. These findings were not localized to the temporal lobe, but appeared in the form of paroxysmal, synchronous break-

throughs more suggestive of a subcortical origin. Klingman and Moore have earlier pointed out that EEG changes of similar "epileptic equivalents" have no characteristic appearance and could even consist of break-throughs of the above-mentioned type rather than having the appearance of something reminiscent of petit-mal variations. Temporal foci may not have been described. Therapy with hydantoin preparations had good effect in the described cases. Abdominal pain attacks can appear as aura preceding an epileptic seizure, when the diagnosis needs not be discussed. If in the meantime the pains represent the sole clinical symptoms, then diagnosis becomes more difficult. If one finds in cases of recurrent abdominal pains EEG changes of a specific nature, such as described above, then one should be entitled to speak of an epilepsy. For similar types of epilepsy the author considers, in conformity with C. H. Snyder, that the designation "epileptic equivalent" is the most suitable one.

A. L. Annell: Relatively many cases with so-called abdominal migraine have been studied in the Child Psychiatric Clinic. In the absence of any somatic cause it is considered that the indisposition often is of "nervous" origin and in many cases it is evident that its occurrence depends on whether or not the child is exposed to any form of stress and strain. A combination of medical and psychological treatment often produces strikingly good results. A detailed assessment of the EEG often supplies good leads as to the proper medical preparations to use on individual cases. At least 3 types of pathological EEG are encountered: (1) Paroxysmal with localization indications; this group often reacts well with hydantoin preparations. (2) Localization in the temporal region, the abdominal attacks in such cases may eventually be apperhended as a form of temporal lobe epilepsy; occasionally this group reacts well with hydantoin preparations, sometimes also with mylepsin and agin with chlorpromazin. (3) The appearance of the curve witnesses to subcortical functional disturbances; this group reacts surprisingly well with chlorpromazin and fentiazin derivatives (Transergan). The most important fact is that EEG is normal in some patients during asymptomatic periods, while it presents a different pathological pattern during periods when the child is indisposed.

A. Wallgren: The speaker has talked about the relationship between epilepsy and attacks of abdominal pains. However, he heads his paper "Abdominal migraine" and maintains that he does so because abdominal migraine sounds less alarming to the patient's relatives than the term abdominal epilepsy. In view of the fact that we are in a quandary as to whether the pains in question are equivalent to epilepsy or to migraine, we may ask why, in the meantime, we should not make use, for the relatives, of the old, rather meaningless and non-prejudicial term of abdominal colic?

Gert v. Sydow: In connection with Hagberg's reported case of recurrent abdominal pains and cyclic vomiting in a 13-year-old girl, in which cholegraphy was abnormal during the attacks, I would like to discuss a very similar anamnesis, with a decidedly different background. A boy, ten years old at present, has since the age of 4 been treated in our clinic 14 times because of severe cyclic attacks of vomiting accompanied with abdominal pains and acidosis. The first attack was provoked by appendectomy. The attacks have usually been induced by psychogenic factors, and we have noticed, moreover, that he gets cramp-like abdominal pains of the same sort if he eats an egg. On the fourteenth visit we noticed a tender area of resistance below the right arcus. Cholecystography disclosed a large sac-like dilatation in the cystic duct. At laparotomy the choledochus duct appeared to empty into the pancreatic duct. A choledochus-duodenostomy was performed. During the subsequent 2 months the boy has been free from symptoms.

***Per Lennart Adner* and *Stig Sjölin:* Transfusion studies with red cells, from newborn infants and adults, labelled with ^{51}Cr.**

Red blood cells from full-term newborn infants were labelled with radioactive chromium (^{51}Cr) and their survival was followed after transfusion to healthy adult subjects. In the 10 cases investigated the biological half-life was found to vary between 17 and 27 days, compared with 22 to 34 days in normal adult controls. In 4 of these 10 cases a half-life of 17 to 20 days was found. The red cells of two premature infants, investigated in the same manner, showed half-lifes of 15 and 10 days. The experiments show that red cells from full-term newborn infants have slightly shortened survival times and red cells from premature infants may have very short survival times. It was concluded that in some newborn infants the physiological anaemia may partly depend on a relatively short life span of the red cells. A preliminary report on other findings concerning the frequency of immunisation after blood transfusions will be published in *Scand. J. Clin. & Lab. Invest.*, 1957.

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BOOK REVIEW

Lehrbuch der Kinderchirurgie. By Dr. *Max Grob* in cooperation with Dr. *Margrit Stockmann* and Dr. *Marcel Bettex*.

761 pages, 876 pictures, some in colour. Price DM 157, Sw. kr. 212.—.

This textbook gives an extensive review of pediatric surgery. It deals with pre- and postoperative treatment, including anesthesia and hibernation. The chapters on the diseases and malformations of the different organ systems are very complete and include an extensive and interesting review of neurological disorders. It is always possible, of course, to find something to criticize in any book under review, and the authors of this book do not in all details agree with the practice in Scandinavian countries. In this instance, however, any critical remarks should be few and of small importance when judging the value of the book. In the opinion of the reviewer, this book is of the greatest value not only to general surgeons and pediatricians but also for more specialized pediatric surgeons. The extremely fine typography and illustrations increase the reader's pleasure. The book is warmly recommended to all those interested in this field of medicine and it is well worth its price.

N. O. Ericsson

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